Title

Relevant domains and outcome measurement instruments in Neuropsychiatric Systemic Lupus Erythematosus: a systematic literature review.

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Abstract

Objectives: Neuropsychiatric involvement in Systemic Lupus Erythematosus (NPSLE) is one of the most complex expressions of the disease, lacking validated outcome measurement instruments to support specific interventions in controlled clinical trials. The objective of this systematic literature review (SLR) is to identify outcome measurement instruments and domains used to assess NPSLE.

Methods: This SLR was performed following Preferred Reporting Items for systematic reviews and Meta-analysis (PRISMA) guidelines. All articles available in English (1967-2018), in PubMed, EMBASE, PsycINFO, Cochrane Library and EULAR outcome measures library were screened. All domains and outcome measurement instruments were characterized according to the OMERACT Filter 2.1, considering core areas (manifestations/abnormalities, life impact, death/lifespan, societal/resource use) and contextual factors.

Results: Of 2,647 abstracts evaluated, 72 studies (1961-2016) were included in the SLR, for a total of 14,068 patients, mainly female (89.7%), mean (SD) age 35.0 (5.7) years. Studies identified included domains and instruments pertinent to all core areas defined by OMERACT, except societal/resource use. The core area most represented was “manifestations/abnormalities” (10 domains), followed by “life impact” (7 domains).

Conclusion: Our study revealed a great heterogeneity in the assessment of NPSLE, and this finding supports the development and further validation of a core domain set and outcome measurement instruments, to promote clinical research in this field, enhancing comparability across studies.

Keywords:

Systemic Lupus Erythematosus, Neuropsychiatric lupus, Outcome measurement instruments, Treatment.

Key messages

- Assessment of Neuropsychiatric involvement in SLE lacks in validated instruments to support specific interventions.

- Domains and instruments pertinent to different core areas defined by OMERACT were identified in NPSLE.

- A great heterogeneity exists in assessing NPSLE outcomes, with no validated core-set of outcome measures.

Introduction

Neuropsychiatric (NP) involvement in Systemic Lupus Erythematosus (SLE) is one of the most complex and severe manifestations of the disease that consists of a heterogeneous variety of neurological and psychiatric syndromes, none of which specific for SLE (1,2,3,4). In 1999, the American College of Rheumatology (ACR) provided standard nomenclature and case sets for the definition of 19 NP syndromes, 12 involving Central (CNS) and 7 Peripheral Nervous System (PNS)(5). Various algorithms for attribution of NP events in SLE has been validated (6,7) and purposed by different groups (8–10). The NPSLE spectrum diseases lack validated outcome measurement instruments to support specific interventions. The absence of standardization for defining response to therapy in NPSLE is one of the most important barriers to test new therapeutic strategies or drugs in randomized controlled clinical trials (RCTs) to such an extent that severe NP involvement is invariably enlisted among exclusion criteria (3,11). In the absence of RCTs, the adoption of glucocorticoids (GCs), immunosuppressants, anticoagulants, symptomatic therapies and non-pharmacological interventions is supported by observational studies, case-series and clinical experience, summarized under the 2010 EULAR recommendations for NPSLE (12), and 2019 EULAR recommendations for SLE management (13). The challenge of proper outcome measurement definition in SLE overcomes the NP involvement. Several SLE therapeutic trials, in fact, have failed to meet pre-designed endpoints, and there is no agreement if this should be partially attributed to suboptimal outcome measurement instruments employed (14). The heterogeneity of SLE makes difficult for any single - or even composite - measure to encompass all the manifestations of the disease and able to capture meaningful improvements in distinct disease phenotypes, such as NPSLE, for which “organ-specific” response criteria are needed (15). This supports the relevance for developing outcome measurement instruments (OMIs) for NPSLE.

According to Outcome Measures in Rheumatology (OMERACT), OMI is defined as a tool chosen to assess outcomes, in terms of quality or quantity of a variable, which can be a single question, a questionnaire, a score obtained through physical examination, a laboratory measurement, etc. (16). The OMERACT filter permits to validate an instrument, applying the concepts of truth, discrimination, and feasibility. To improve content validity, OMERACT Filter 2.0 (17) and 2.1 (18) defined a framework characterized by different concepts (pathophysiology, impact), core areas (death/lifespan, life impact, societal/resource use, manifestations/abnormalities), and disease-specific domains pertinent to the core area. A core domain set reflects the presence of at least one domain inside each core area, with at least one validated OMI inside each domain. OMERACT advises incorporating the core outcome measurement set developed for each condition in all RCTs. Since no previous study has specifically analyzed how disease outcomes were assessed in NPSLE, we performed a systematic literature review (SLR) with the main aim to identify all possible domains and OMIs evaluated in NPSLE applying the OMERACT Filter 2.1 framework.

Materials and Methods

Systematic literature review

A search was made in Medline (via PubMed), Embase, PsycINFO, Cochrane Library and EULAR outcome measures library using a highly sensitive methodological search filter to find studies on measurement properties of measurement instruments across literature [https://omeracthandbook.org/](16,18–21) (Supplementary Material 1.1a-c). The start date for the literature search was June 1967, the end date was March 1st, 2018. The SLR considered studies in the English language, including adult patients (aged ≥16 years) with NPSLE (clinical NPSLE or defined by NPSLE-ACR nomenclature (5)), any outcome measures. The SLR considered only RCTs, SLRs and meta-analyses, cohort, case-control studies, and case-series (>5 patients) available in full text. We excluded congress proceedings and abstracts; duplicate publications; case reports; letters to the editor and narrative reviews. Papers were screened blindly by 4 reviewers (ES, EC, FB, MEDA). In the first step, the selection was based on titles and abstracts. Full reports of articles selected in this phase were evaluated to retrieve articles for final inclusion in this SLR. The electronic search was completed by the screening of the reference list of all identified articles and hand-search of articles cited in thematically relevant reviews and by sources provided by the steering committee. Disagreement regarding the inclusion of an article was discussed between reviewers until consensus was reached. Persistent disagreements were resolved by a fifth evaluator (AB). Data retrieved were recorded using a secure electronic data-capture database on a pre-specified extraction form (22). Data extracted included information on study design, sample size, gender, follow-up period of interventions, disease duration, NP manifestations, study methods, and outcomes, related to the review question and specific objectives. All domains and OMIs were evaluated using the OMERACT Filter 2.1 framework (18–20), following OMERACT handbook (16), and summarized qualitatively. This SLR was conducted in accordance with the Preferred Reporting Items for systematic reviews and Meta-analysis (PRISMA) statement (Supplementary Material 1.1d).

Statistical analysis

Descriptive results of the SLR were reported as mean and standard deviation (SD) for quantitative variables. Qualitative analyses of domains and OMIs were performed according to core areas defined by OMERACT (manifestations/abnormalities, life impact, death/lifespan, societal/resource use), and contextual factors (18). Analyses were performed using the Stata14 software (STATA Corporation, College Station, Texas, USA).

Results

Of 2,647 abstracts evaluated, 72 studies were included in the SLR (Fig.1), of which one RCT (1.4%, 32 patients), 5 SLRs (6.9%, 8,056 patients), 26 cohort studies (36.1%, 4,560 patients) and 40 observational studies (55.6%, 1,420 patients), with a total of 14,068 patients (Table 1). Studies retrieved refer to data obtained between 1961 and 2016. Studies identified in the SLR included domains and instruments pertinent to all core areas defined by OMERACT (18), except societal/resource use. The core area most represented was "manifestations/abnormalities" structures in 10 domains, followed by "life impact" in 7 domains (Table 2, Fig.2).

Core area - manifestations/abnormalities

Domain - laboratory markers

Laboratory markers including serological, peripheral blood, and cerebrospinal fluid (CSF) were assessed in 8 studies, including 120 patients. In 5 studies serological markers were secondary outcomes of response to rituximab (RTX) in refractory NP manifestations: all studies analyzed the increase (23–26) or normalization (27) of serum complement levels, 3 studies evaluated the reduction (25,26) or normalization of anti-double stranded-DNA antibodies (anti-dsDNA) levels (24) and 1 study the lowering of immunoglobulins titers (25). Complement levels were also longitudinally evaluated in a RCT comparing the response to cyclophosphamide (CYC) versus GCs (28). One study analyzed neuromyelitis optica (NMO)-IgG titers fluctuation after immunosuppressive treatment in SLE-related myelopathy and no variation was observed (29). Considering cellular biomarkers, 4 studies correlated peripheral CD19+ (23,24), naïve, memory B cells, plasmablasts (25,26) and CD19+CD40+ and CD19+CD80+ values (23) with clinical response to RTX, suggesting that longitudinal assessment of cellular subpopulations could be exploited to monitor disease activity after this specific therapy. Total leukocytes/lymphocytes count was assessed in one study following CYC and GCs treatment, with no significant variation between the two arms (28). Finally, 2 studies evaluated CSF markers. In one open label study, the levels of CSF Interleukin (IL)-6 (23) did not change whilst the CSF IgG-index improved after RTX treatment. A prospective analysis from a cross-sectional study suggested the potential role of CSF biochemical markers of brain inflammation: NPSLE patients successfully treated with CYC exhibited a reduction in CSF levels of neurofilament triplet protein (NFL) and glial fibrillary acidic protein (GFAP) (30).

Domain - instrumental markers

Among instrumental markers, conventional brain and spinal cord magnetic resonance imaging (MRI) was employed in 22 studies (23,26,28,31–49). Lupus myelopathy (LM) was the most frequently assessed NP manifestation (14 studies, 63.6%). Globally, MRI was judged as altered or normal, with only one study investigating the specific role of selected MRI abnormalities (36). Correlation with clinical response has rarely

been investigated, with contrasting results. Overall, conventional MRI allowed predicting clinical course of the disease only in some cases (evidence of large alterations, gadolinium-enhancements or cortical lesions), with evidence of MRI amelioration correlating with clinical NP improvement during follow-up in three studies (28,36,41). In two cases MRI lesion load stability has been considerate as a surrogate positive biomarker (42,43). Partial or complete recovery of MRI findings was highlighted in less than 50% of cases of NP syndromes improvement (23,42,44). In myelopathies, spinal cord MRI repeated through follow-up gave unclear correlation with clinical the response: MRI lesions persisted in patients lacking in response to treatment (40), while reduction/disappearance of lesions was not always positively related to the clinical gain of function (33,35,39,40).

Analysing quantitative brain MRI techniques, magnetization transfer imaging (MTI) was assessed in 3 studies (50–52). Whole brain magnetization transfer ratio - histogram peak height (MTR-HPH) was associated to neurologic and psychiatric functioning in NPSLE subjects (51); at white matter (WM) level, changes across follow-up in mean MTR-HPH positively correlated with clinical improvement of patients with active NPSLE manifestations at baseline visit (50). Cerebral metabolites ratios, measured using magnetic resonance spectroscopy (MRS), were assessed in 5 studies (45–47,49,53). N-acetylaspartate/Creatine (NAA/Cr) ratio measured with single-voxel MRS increased following successful clinical management of NPSLE.

Other neuroimaging techniques evaluated were brain computed tomography (CT) in one study (54), single photon emission computed tomography (SPECT) in 6 (23,26,32,42,55,56) and positron emission tomography (PET) in 2 (23,57). In a case series of 14 NPSLE patients for whom baseline and follow-up PET scans were available (57), clinical improvement associated with improvement or normalisation of specific regions of hypometabolism (8 cases), while symptoms worsening associated with PET deterioration (2 patients). SPECT, was used to monitor treatment response in NPSLE, in particular, when the baseline scan was altered, cerebral blood flow increased following clinical improvement (23,26,42,55,56).

Neurophysiology outcome measurement instruments included electroencephalography (EEG), evoked potentials (EPs), electromyography (EMG). EEG was evaluated in 4 studies (28,34,58,59): quantitative EEG improvement during follow-up (58) was in line with clinical improvement of different major NP events (5 out of 6 patients). In a RCT (28) determining the best treatment for severe NPSLE, all the 6 patients with seizures in the CYC group showed EEG improvement, while only 2 out of 5 in the GC arm. EPs and EMG findings improved in the CYC-treatment arm in patients with polyneuropathy and brainstem disease, in line with treatment response (28). Stojanovich et al. (59), similarly, demonstrated that EEG and EPs were useful in the longitudinal assessment of patients with primary NPSLE, mainly in patients treated with CYC with respect to GCs. Clinical improvement occurred in 28 out of 60 patients, EEG recovery in 26/58 patients and EPs recovery in 20/55 patients. Regarding EMG (28,34,59,60), a multicentre study of SLE patients with multiple mononeuropathy (60) showed that EMG sensory-motor sequelae were present in the majority of patients at follow-up evaluation.

Domain - composite measures: disease activity

Outcome measurement instruments related to SLE disease activity included SLEDAI-2K (4 studies), SLEDAI (13 studies), European Consensus Lupus Activity Measurement (ECLAM) (2 studies), SELENA-SLEDAI (4 studies) and BILAG (4 studies). Only in five studies, they were used to measure NP manifestations response after a specific treatment (RTX)(23–25,27,42). Considering ECLAM, a retrospective study has shown ECLAM score reduction after prompt treatment for severe NPSLE (41), while, similarly to SLEDAI, no differences were found during more prolonged follow-up periods (61). Two studies did not show a correlation between disease activity indexes and other comparators, such as the activity of specific symptoms (e.g. headache) or quantitative EEG measures (58,62).

Domain - relapse

Different NP syndromes were evaluated for relapses, mainly in observational studies. LM (6 studies) and seizures (5 studies) were the manifestations most frequently assessed. SELENA Flare Index (SFI) measured NPSLE relapses in a cohort study of patients treated with RTX (24). Considering specific NP syndromes, 17 studies assessed relapses applying its own definition each (Table 3). B-cells levels after RTX therapy correlated with moderate flares (25), while a SLR highlighted a strong correlation between anti-phospholipid antibodies (aPL) positivity and overall risk of NP syndromes relapse (63).

Domain - composite measures: damage

Quantification of global damage was also measured, specifically through Systemic Lupus International Collaborating Clinics (SLICC) ACR Damage Index (SDI) in 6 studies (24,28,34,61,62,64).

Other domains

Other relevant domains pertaining to “manifestations/abnormalities” core area refer to cognitive, sensory-motor, depression-anxiety, psychiatric, and pain fields, with several OMIs enlisted for each domain (Table 2).

Core area - Life impact

Domain physician global assessment

The impact of NP manifestations in daily life was investigated through different outcome measures exploring the clinical response to treatment in terms of patients’ reported activity, fatigue, neurological function, and quality of life (QoL). Likert scale is a rating scale used to measure physician’s attitudes on NP clinical outcome: Hanly et al. proposed a seven-point Likert scale (from 1=death to 7=resolved) to assess the outcome of NP events (65–70). Simplified 4-points (71) and 5-points scales (72) were also used. Neuwelt's criteria were introduced (73,74) to define clinical outcomes of severe NPSLE patients after CYC therapy and were assessed in 6 studies (389 patients). Outcomes were categorized in 3 (improved, stabilized and progressed)(44,73–75)

or 2 groups (responders and non-responders)(32). Barile-Fabris et al. (28) specified that improvement or worsening should retain at least a 20% change from basal conditions. Other definitions for PhGA were used to define clinical response to treatment in 34 studies for a total of 1,280 NPSLE patients (Table 4). PhGA distinguished between good (complete or partial recovery) and bad response (worsening, relapses, or death) occurred between the first and the last visit (mean (SD) follow-up period 1,169 (1,492 days)).

Domains: Glasgow Coma Scale, PGA, fatigue and function

Glasgow Coma Scale (GCS), a neurological scale which records the state of person's consciousness, was assessed in an open label study including 5 patients suffering from acute confusional state to monitor RTX response (23). Considering Patient Global Activity (PGA), Patient's Assessment of Own Functioning Inventory (PAF), a subjective neurocognitive questionnaire, was used in a cross-sectional study to compare behavioural correlates between NPSLE and non-NP controls (76). Regarding fatigue, the Fatigue Severity Scale (FSS) and the Modified Multidimensional Assessment of Fatigue (MAF) Questionnaire were evaluated in a longitudinal study (76), in which a correlation between fatigue impact on daily life and cognitive impairment was found. Other tools permitted the quantification of the different degrees of neurologic impairment potentially occurring in NPSLE (Table 2).

Domain quality of life

To assess QoL, two self-administered questionnaires were used. The EuroQol-5D questionnaire was assessed in a cross-sectional study on 33 patients with variable NP syndromes (77). The Medical Outcome Study Short Form 36 (SF-36) was administered to 3,795 heterogeneous NPSLE patients in 11 studies (1 SLR, 1 cross-sectional and 9 longitudinal studies)(26,62,65–71,78,79).

Domain hospitalization

Hospitalization was assessed in 2 observational studies (25,80). One retrospective study considered the rate of re-admission to hospital related to neurological relapse as a measure of outcome for NPSLE (80), while a second study retrieved also hospitalizations due to adverse events of SLE treatments (25).

Core area – Death/lifespan

Domain mortality

18 studies addressed death and mortality as appropriate OMIs. Mortality was assessed as related to NP manifestations themselves (2,81), as well as connected to specific treatments (73,74). Moritani et al. described association of death with a specific brain diffusion-weighted imaging MRI pattern corresponding to vasogenic oedema (82).

Core area - Contextual factors

Domain adverse events

Adverse events (AEs) and side effects of SLE therapies were recorded in 14 studies. The most frequent types of AEs recorded were severe infections, or specific drugs-related AEs (e.g. hypertension, Cushingoid features, alopecia, neoplasms)(23,28,48,73,83).

Domain glucocorticoid therapy

Finally, GCs dosage reduction was investigated as outcome in 7 studies (24,26–28,34,42,64). Steroid dosage was gradually reduced after RTX treatment, mainly in responders than in non-responders; however, pooled-data for NPSLE subjects were not available in these studies (24,42). The corticosteroid-sparing effect of CYC versus methylprednisolone pulses was demonstrated after 6 and 15 months in a RCT (28).

Discussion

NPSLE is a heterogeneous condition, and one of the major unmet needs is to define reliable outcome measures, to capture the effect of different interventions (3,11). To the best of our knowledge, this SLR is the first attempt of systematic recognition of different domains and OMIs adopted in the evaluation of NPSLE patients. This SLR demonstrates that a great heterogeneity exists in the assessment of NPSLE. According to OMERACT (18), there is a need to provide core sets of OMIs, capable to provide consistent estimates of the benefits of interventions for different conditions in RCTs. Core outcome measurement sets should contain instruments pertinent to different domains included in a core domain set, with at least one domain inside each core area. The objective is to define core domain sets and core outcome measurement sets to be included in all RCTs in a definite clinical condition (16). To this end, the assessment of outcome measures in NPSLE has not been undergone so far, with most of evidence derived from observational studies. Applying a systematic search of available literature, we have performed an exploration of different outcome measures previously used to assess NPSLE disease activity and treatment response. The most frequently assessed core areas were "manifestations/abnormalities" and "life impact". Different domains were examined, ranging from laboratory/instrumental methods, to physicians or patients perceived disease activity, to specific cognitive or psychiatric fields. Going deeply into the significance of single OMIs, the most frequently assessed were PhGA (34 studies), conventional brain or spinal cord MRI (22), death/mortality (18), NP symptoms recurrence (17), and AEs (14). However, characterization of PhGA or recurrence was not homogeneous, and some studies did not report exact definitions (33,84,85). Some studies adopted Likert scales or Neuwelt's criteria, but stratification of patients according to these tools was not univocal (66,71,72). Regarding MRI, few studies specifically addressed the significance of elementary lesions (36), while the majority roughly evaluated the modifications of imaging patterns, describing repeated MRI scans as ameliorated, stable, or worsened. Among quantitative MRI techniques, MTI, which indirectly reflects the integrity of macromolecular structures (e.g. myelin), and MRS, which measures the ratios of different cerebral metabolites, were used to assess treatment responses (45,50). Nevertheless, low-rate clinical application, as well as absence of standardization and homogenization in data analysis, claim for further validation of such procedures (86). In SPECT studies (23,26,32,42,55,56), mean number of patients included was low (24.2, SD 9.2), similarly to other neuroimaging or neurophysiological studies. Composite disease activity measures (e.g. SLEDAI) were mainly used in longitudinal studies including other non-NPSLE patients (24–27), reflecting a possible perception that these indexes might not be able to capture meaningful modifications in single-organ (e.g. CNS) activity. Again, relatively few studies assessed GC dosage reduction, as well as specific patients' perception of disease activity. SF-36 remained the most frequently adopted measure to capture modifications in physical and mental dimensions (65,71). Given this large heterogeneity, there is claim to prioritize NPSLE domains according to OMERACT frameworks, to define a core domain set, and to finally

apply, to each outcome measure included, the concepts of truth, discrimination and feasibility, the main properties that need to be addressed in order to validate an instrument and to include it in clinical trials (16).

This study has some limitations, for example the lack of standardized evaluation of the quality of studies retrieved. In fact only one RCT was included (28), with overall quality judged as moderate (34). Secondly, it was out of the scope of this SLR the characterization of specific properties of OMIs (truth, feasibility and discrimination)(16,20), and this aspect should be investigated in following works. It was not always possible to capture transitions among different NP states over time, such as maintaining active NP symptoms status, turning inactive or facing relapses (11).

In conclusion, our study revealed a relevant heterogeneity and lack of properly validated outcome measures in the assessment of NPSLE. These findings support the prioritization and definition of core domains and outcome measurement instruments to provide reliable tools to be used in daily clinical practice and to be included in RCTs, in order to promote clinical research in this field, enhancing comparability among studies.

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No

Conflicts of Interest

The authors declare no conflicts of interest.

Data access

The authors have full control of all primary data and agree to allow the journal to review data if requested.

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Authors' contribution

All the authors have made substantial contributions to the conception or design of the work, or acquisition, analysis, interpretation of data; have drafted the work or revised it critically for important intellectual content; finally approved the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethical standards

The manuscript does not contain patient data.

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Tables and Figures

Table 1. Descriptive results (72 included articles).

Variables	Frequency	
Number of studies, N (%)	All studies	72 (100%)
	RCT	1 (1.4%)
	SLR/meta-analysis	5 (6.9%)
	Cohort study	26 (36.1%)
	Other observational	40 (55.6%)
Number of participants, N (±SD)	All studies	14,068 (198.14± 957.6)
	RCT	32
	SRL/meta-analysis	8,056 (2,014± 3,990.7)
	Cohort study	4,560 (175.38± 285.9)
	Other observational	1,420 (35.5± 45.8)
Mean age, years (±SD)		35.0± 5.7
Female, mean percentage		89.7
Mean disease duration, years (±SD)		5.2± 2.5
Mean follow up, months (±SD)		961.9± 1,222.9
NPSLE manifestations, N of studies (%)	Aseptic meningitis	18 (25%)
	Cerebrovascular disease	36 (50%)
	Demyelinating syndrome	18 (25%)
	Headache	35 (48.6%)
	Movements disorders	21 (29.2%)
	Myelopathies	35 (48.6%)
	Seizure disorders	40 (55.6%)
	Acute confusional state	28 (38.9%)
	Anxiety disorders	18 (25%)
	Cognitive dysfunction	29 (40.3%)
	Mood disorders	36 (50%)
	Psychosis	36 (50%)
	Acute inflammatory polyradiculoneuropathy	6 (8.3%)
	Autonomic disorder	6 (8.3%)
	Mononeuropathy	21 (29.2%)
	Myasthenia gravis	7 (9.7%)
	Cranial neuropathy	29 (40.3%)
	Plexopathy	5 (6.9%)
	Polyneuropathy	24 (33.3%)
	Others	5 (6.9%)

List of abbrevations: RCT, Randomized clinical trial; SLR, Systematic literature review; SD, Standard deviation; NPSLE, Neuro-Psychiatric Systemic Lupus Erythematosus.

Table 2. Domains and instruments pertinent to core areas defined by OMERACT Filter 2.1 (18), reported in the 67 selected articles.

Concepts	Core Areas	Domains	Instruments	N. of Studies Using the Instrument	Ref.
Pathophysiology	**Manifestations / Abnormalities**	**Laboratory markers**	• Complement levels	6	(23–28)
			• Anti-dsDNA	3	(24–26)
			• Anti-NMO IgG	1	(29)
			• Immunoglobulins (IgM, IgA, IgM) titer	1	(25)
			• Peripheral blood B cell subsets	2	(24,25)
			• Expression of functional molecules on CD4-positive cells (CD40L, ICOS; CD69, CD4)	1	(23)
			• PBMCs CD40-expressing and CD80-expressing CD19-positive cells, CD20-positive cells	2	(23,26)
			• Total leukocytes/lymphocytes count	1	(28)
			• CSF Interleukin (IL)-6 level	1	(23)
			• CSF IgG Index	1	(23)
			• CSF GFAP level	1	(30)
			• CSF NFL	1	(30)
		Instrumental markers	• Fundoscopy	1	(83)
			• Field test	1	(83)
			• Electrophysiological studies (EMG)	4	(28,34,59,60)
			• EEG	4	(28,34,58,59)
			• Evoked Potentials	3	(28,34,59)
			• Brain computed tomography	1	(54)
			• Brain/spinal cord MRI	22	(23,26,28,31–49)
			• MTR-HPH	3	(50–52)
			• MRS	5	(45–47,49,53)
			• SPECT	6	(23,26,32,42,55,56)
			• 18FDG-PET	2	(23,57)
		Cognitive field	• ACR-SLE battery	1	(76)
			• MMSE	2	(34,87)
			• HDS-R	1	(42)
			• Cognitive Failures Questionnaire	1	(76)
			• Wechsler Adult Intelligence Scale	1	(51)
		Sensory-motor field	• ASIA Impairment Scale	1	(88)
		Depression/Anxiety field	• CES-D	1	(76)
			• HAM-D	4	(34,42,62,87)
			• HAM-A	1	(62)
			• HADS	1	(51)
		Psychiatric field	• BPRS	4	(23,34,42,87)
			• YMRS	1	(42)
		Pain	• The Short-Form McGill Pain Questionnaire	1	(76)
		Composite measures - Disease activity	• SLEDAI-2K	4	(26,32,64,69)
			• SLEDAI	13	(23,26,28,34,41,42,45–47,53,58,61,77)

			• SELENA-SLEDAI	4	(24,26,27,62)
			• ECLAM	2	(41,61)
			• BILAG	4	(25,26,42,88)
		Relapse	• SFI	1	(24)
			• Own definition	17	(24–27,34,39,44,59,60,62,63,84,88–92)
		Composite measures - Damage	• SDI	6	(24,28,34,61,62,64)
Impact	**Life impact**	**PhGA**	• Likert scale (7-, 5- or 4-points scale)	8	(65–72)
			• Neuwelt's response criteria	6	(28,32,44,73–75)
			• Clinical response (own definition)	34	(23,24,26,27,31,33–37,39–43,48,50,52,54,57,59,61,62,64,78,84,85,87,89–91,93–95)
		GCS	• GCS	1	(23)
		PGA	• Patient's Assessment of Own Functioning Inventory	1	(76)
		Fatigue	• FSS	1	(76)
			• MAF	1	(76)
		Function	• EDMUS-GS	1	(35)
			• EDSS	2	(29,51)
			• modified Rankin Scale	2	(60,71)
			• Walking Index for Spinal Cord Injury	1	(88)
			• Visual acuity	2	(28,83)
		Quality of life	• SF-36	11	(26,62,65–71,78,79)
			• EuroQol-5D questionnaire	1	(77)
		Hospitalization	• Number	2	(25,80)
	Death/Lifespan	**Mortality**	• Death, mortality, mortality rate	18	(2,24–27,29,34,37,64,73–75,80,81,84,87,89,90)
	Societal / Resource use	-	-	0	-
Contextual factors		**Adverse events**	• General	14	(23,24,26–28,34,41,42,48,59,73,74,83,88)
		Glucocorticoid therapy	• Minimal dose, GC reduction	7	(24,26–28,34,42,64)

List of abbreviations: anti-NMO, neuromyelitis optica-IgG; anti-dsDNA, anti-double stranded DNA antibodies; PBMCs, peripheral blood mononuclear cells; EEG, electroencephalogram; CSF, cerebrospinal fluid analysis; GFAP, glial fibrillary acidic protein; neurofilament triplet protein, NFL; MRI, magnetic resonance imaging; MTR-HPH, magnetization transfer ratio histogram peak height; MTI, magnetization transfer imaging; SPECT, single photon emission computed tomography; PET, 18FTG-positron emission tomography; GCS, Glasgow coma scale; PhGA, physician global assessment; PGA, patient global assessment; MMSE, mini mental state examination; HDS-R, Hierarchic Dementia Scale-Revised; ASIA, American Spinal Injury Association; CES-D, Center for Epidemiologic Studies Depression Scale; HAM-D, Hamilton Depression Rating Scale; HAM-A, Hamilton Rating Scale for Anxiety; HADS, Hospital Anxiety and Depression Scale questionnaire; BPRS, Brief Psychiatric Rating Scale; YMRS, Young Mania Rating Scale; HDS-R, Hierarchic Dementia Scale-Revised; HAM-D, Hamilton Depressive Score; FSS, The Fatigue Severity Scale; MAF, Modified Multidimensional Assessment of Fatigue Questionnaire; EDMUS-GS, European Database for Multiple Sclerosis grading scale; EDSS, Expanded Disability Status Scale; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index 2000; SFI, SELENA-SLEDAI Flare Index; ECLAM, European Consensus Lupus Activity Measurement; BILAG, British Isles Lupus Assessment Group index; SDI, The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; SF-36, Short Form (36) health survey; GC, glucocorticoid.

Table 3. Specific definitions for relapses of clinical NP syndromes, according to studies retrieved in the SLR.

Definition of relapse for NP manifestations	Number of studies	Ref.
SFI	1	(24)
Exacerbations of NP syndromes	2	(84,88)
Recurrent or new NP events	2	(27,44)
Psychotic flare	1	(91)
Relapse of symptoms	6	(26,39,59,60,89,90)
Recurrent NPSLE	1	(63)
Flares defined as a new BILAG grade A (not present at baseline), or a new grade B	1	(25)
Number of seizures per month	1	(34)
SLE flare	3	(26,62,92)

List of abbreviations: NP, neuro-psychiatric; SLR, systematic literature review; SFI, SELENA-SLEDAI Flare Index; SLE, Systemic Lupus erythematosus.

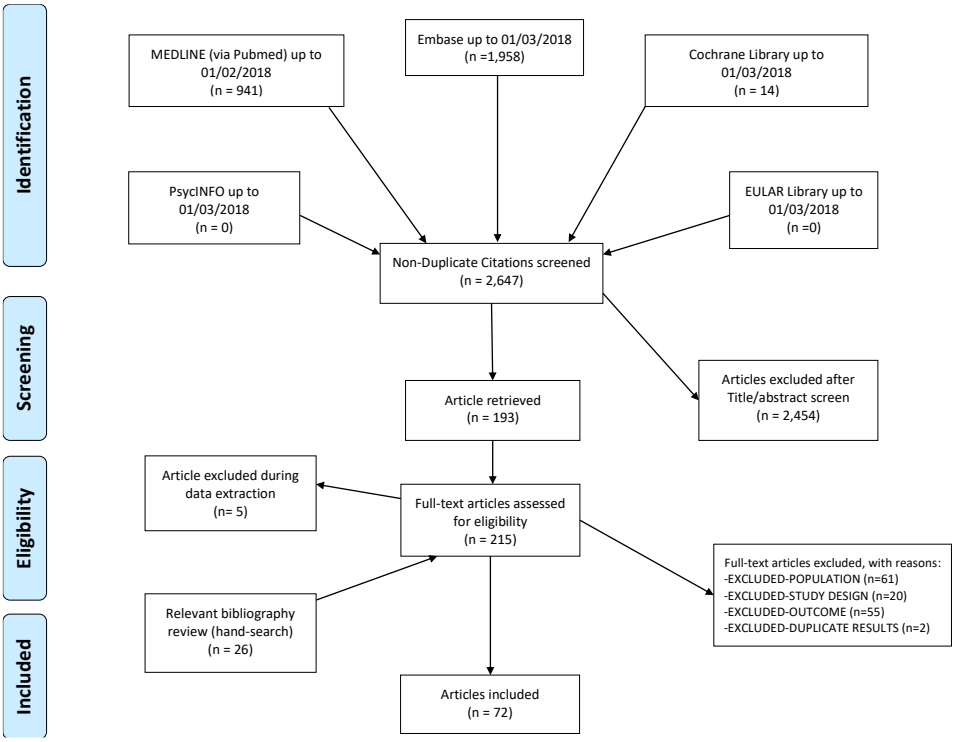
Table 4. Specific definitions for physician global assessment for NPSLE, according to studies retrieved in the SLR.

Definition of physician global assessment for NPSLE	N° of studies	Ref.
Likert scale (7-, 5- or 4-points scale)	8	(65–72)
Neuwelt's response criteria	6	(28,32,44,73–75)
Good response: complete improvement of neuropsychiatric symptoms without any sequelae; partial response: initial improvement with later exacerbation and/or incomplete improvement with sequelae; poor response: no improvement and/or exacerbations.	1	(31)
Active/inactive NPSLE	1	(54)
Generic description of symptoms improvement	1	(39)
Generic description of response to treatment	2	(33,84)
Symptoms resolution	1	(85)
Motor, sensory and sphincter recovery	1	(48)
Arbitrary 3-level categorical outcome as improved, stable, or worse	1	(93)
Improvement of symptoms and presence of any neurologic sequelae	1	(64)
Psychosis remission	1	(91)
Complete/partial resolution of symptoms, absence of improvement	2	(35,40)
Complete resolution of symptoms, improvement, no change, worsening	1	(57)
Symptoms improved/stable/worsened	1	(43)
Resolution, improvement, stability of symptoms AND neurological examination	1	(82)
Complete remission: all the signs and symptoms had completely disappeared; partial remission: symptoms had improved, but at least one persisted (sign and/or symptom); no response: the clinical manifestations remained unchanged or deteriorating	1	(94)
Symptoms present/ameliorated/worsened/absent	1	(61)
Improvement through clinical appraisal	2	(34,87)
Presence/absence of new seizures	1	(95)
Clinical improvement of CNS lupus: either sustained complete recovery or recovery with minor residual deficits that no longer required hospitalization; stabilization: status in which no new clinical (i.e., neurologic or psychiatric) abnormalities occurred, although the previous abnormalities remained; deterioration: status in which previous neuropsychiatric symptoms were exacerbated or new ones developed during follow-up	1	(36)
"Improved" status: at least 50% recovery of signs and/or Symptoms; "no response": less than 50% recovery; "worse": progression of the condition.	1	(78)
Presence of major refractory and persistently active events	1	(41)
Improvement in clinical condition established by both the patient and the doctor	1	(59)
Change in clinical NP status defined as worse, stable, or improved by multidisciplinary consensus	2	(50,52)
Major clinical response: achievement of BILAG C scores or better; partial clinical response: achievement of a maximum of one domain with BILAG B score; no clinical response: failure to meet the definition of major or partial clinical response at one or five years.	1	(42)
Neurological examination to define functional response	2	(27,89)
Improvement in symptoms and consciousness state	1	(23)
Patient survived, expired, relapsed	1	(90)
Complete response: SELENA-SLEDAI score of two points or less and a modified SFI score of zero; partial response: reduction of at least four points in the SELENA-SLEDAI score with no new or worsening symptoms as measured by the SFI	1	(24)

Definition not explicated	2	(26,62)

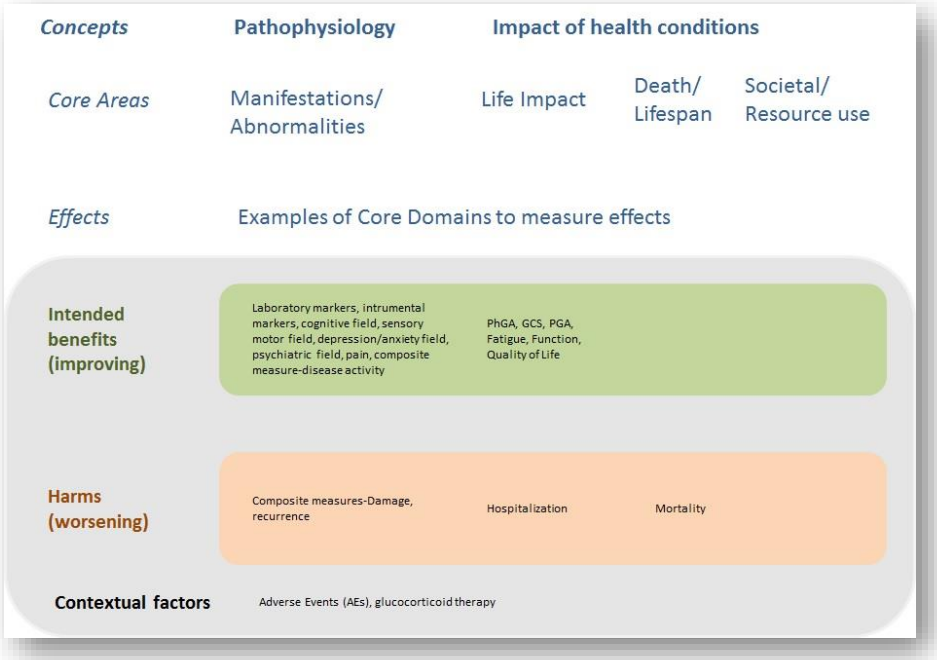
List of abbreviations: NPSLE, neuro-psychiatric systemic lupus erythematosus; SLR, systematic literature review; CNS, central nervous system; BILAG, British Isles Lupus Assessment Group index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI); SFI, SELENA-SLEDAI Flare Index.

Figure 1. Flow-chart. Identification of studies investigating relevant domains and outcome measurement instruments in NPSLE.



NPSLE: Neuro-Psychiatric Systemic Lupus Erythematosus.

Figure 2. Application of OMERACT Filter 2.1 framework (18) to NPSLE.



Commentato [MP1]: La mia impressione è che la figura non sia immediatamente comprensibile.

Forse si potrebbero rafforzare in grassetto o con altro elemento visivo ***Core areas*** and ***Effects*** e minimizzare la frase (*examples of core domains to measure effects*) che è più un testo propedeutico a spiegare quanto è racchiuso nel riquadro colorato, ma ha lo stesso impatto visivo delle varie core areas che anche loro meritano un rafforzativo. Effects potrebbe essere sostato dentro il riquadro colorato ??