Title

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

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Abstract

Objectives: Although neuropsychiatric involvement in Systemic Lupus Erythematosus (NPSLE) is one of the most complex and troubling manifestations of the disease, validated outcome instruments to be used as sensitive endpoints in controlled clinical trials are lacking. We set out a systematic literature review (SLR) to identify outcome measurement instruments and domains used to assess NPSLE.

Methods: The Preferred Reporting Items for systematic reviews and Meta-analysis (PRISMA) guidelines were used. Articles available in English (1967-2020), listed 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 3,392 abstracts evaluated, 83 studies were included in the SLR (15,974 patients, females 89.9%). Eligible studies included domains and instruments pertinent to all core areas defined by OMERACT, except for “societal/resource use”. The most common core areas were “manifestations/abnormalities”, covering 10 domains pertinent to laboratory and instrumental markers, indexes and neuropsychiatric dimension (cognitive, neurologic and psychiatric field), and “life impact”, covering 7 domains related to physical function (from both the perspective of the patient and the physician), pain and quality of life.

Conclusion: Our study revealed great heterogeneity in the instruments derived from populations with NPSLE and none of these had high-quality evidence. This supports the need to develop and further validate 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 NPSLE lacks validated instruments to support specific interventions in trials and clinical practice.

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

- A great heterogeneity exists regarding the instruments used to assess NPSLE, without validated outcome measures.

Introduction

Neuropsychiatric (NP) involvement in Systemic Lupus Erythematosus (SLE) is one of the most complex and severe manifestations of the disease and comprises a heterogeneous set of neurological and psychiatric syndromes (1–3). In 1999, the American College of Rheumatology (ACR) provided standard nomenclature and case definitions for 19 NP syndromes, 12 involving Central (CNS) and 7 Peripheral Nervous System (PNS) accredited as part of SLE (4). Various algorithms for attribution of NP events in SLE have been purposed and validated (5,6) by different groups (7–9), however, the NPSLE spectrum disease lacks validated outcome measurement instruments to support specific interventions in clinical settings. The absence of standardization for defining response to therapy 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 (2,10). 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 EULAR recommendations for NPSLE (11) and SLE (12) management. Moreover, the challenge of proper outcome measurement definition in SLE overcomes the NP involvement. Several SLE therapeutic trials have failed to meet pre-designed endpoints, and there is no agreement to what extent this is due to suboptimal outcome measurement instruments employed (13). The heterogeneity of SLE makes difficult for any single - or even composite - measure to encompass all possible manifestations and to be able to capture meaningful improvements in distinct disease phenotypes, such as NPSLE, for which “organ-specific” and, even more, “individual NP events-specific” response criteria are needed (14). 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, laboratory measurement, etc. (15). The OMERACT filter permits to validate an instrument, applying the concepts of truth, discrimination and feasibility. To improve content validity, OMERACT Filter 2.0 (16) and 2.1 (17) 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 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 instruments across literature [https://omeracthandbook.org/](15,17–20) (Supplementary Material 1.1a-c). The start date for the literature search was June 1967, the end date was June 1st, 2020. The SLR considered studies in the English language, including adult patients (aged ≥16 years) with NPSLE (clinical NPSLE or defined by NPSLE-ACR nomenclature (4)), any outcome measures. We considered only RCTs, SLRs and meta-analyses, cohort, case-control studies, and case-series (>5 patients) available in full text. Congress proceedings and abstracts; duplicate publications; case reports; letters to the editor; editorials; and narrative reviews were excluded. Papers were screened blindly by 4 reviewers (ES, EC, FB, MEDA). The abstracts were divided in two groups and screened independently by two reviewers for each group (ES, MEDA and EC, FB). In the first step, the selection was based on titles and abstracts. Disagreement regarding the inclusion of an article was discussed between reviewers until consensus was reached. Persistent disagreements were resolved by a fifth evaluator (AB). 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. Data retrieved were recorded using a secure electronic data-capture database on a pre-specified extraction form (21). Data were extracted blindly by reviewers with the same subdivision as for title and abstract screening. Disagreement regarding data to be included was discussed between reviewers until consensus was reached. Persistent disagreement was resolved by a fifth evaluator (AB). Included information referred to 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 (17–19), following OMERACT handbook (15), and summarized qualitatively. The standardized evaluation of the quality of studies retrieved was out of the scope of this SLR. 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 (17). Analyses were performed using the Stata14 software (STATA Corporation, College Station, Texas, USA).

Results

Of 3,392 article abstracts evaluated, 83 studies were included in the SLR (Fig.1), of which 3 RCTs (3.6%, 93 patients), 5 SLRs (6.0%, 8,056 patients), 33 cohort studies (39.8%, 6,337 patients) and 42 observational studies (50.6%, 1,488 patients), totalling 15,974 patients (Table 1). Studies retrieved refer to data obtained between 1961 and 2018. Studies identified in the SLR included domains and instruments pertinent to all core areas defined by OMERACT (17), 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 10 studies, including 138 patients. In 5 studies, serological markers were secondary outcomes of response to rituximab (RTX) in refractory NP manifestations: all studies analyzed the increase (22–25) or normalization (26) of serum complement levels, 3 studies evaluated the reduction (24,25) or normalization of anti-double stranded-DNA antibodies (anti-dsDNA) levels (23) and 1 study the lowering of immunoglobulins titers (24). Complement levels were also longitudinally evaluated in a RCT comparing the response to cyclophosphamide (CYC) versus GCs (27) and in a second RCT exploring the effect of low-dose GCs versus placebo (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+ (22,23), naïve, memory B cells, plasmablasts (24,25) and CD19+CD40+ and CD19+CD80+ values (22) 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 (27). Finally, 3 studies evaluated CSF markers. In one open-label study, the levels of CSF Interleukin (IL)-6 (22) 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). CSF osteopontin levels (both full-length and N-terminal fragment) significantly reduced after immunosuppressive treatment for active NP involvement (31).

Domain - instrumental markers

Among instrumental markers (Table 2), conventional brain and spinal cord magnetic resonance imaging (MRI) were employed in 22 studies (22,25,27,32–50). Lupus myelopathy (LM) was the most frequently assessed NP manifestation (14 studies, 63.6%). No standardized protocol of MRI data analysis was highlighted. Globally,

MRI was judged as altered or normal, with only one study investigating the specific role of selected MRI abnormalities (37). Correlation with clinical response has rarely been investigated, with contrasting results. Overall, conventional MRI predicted the clinical course of the disease only in a few cases (evidence of large alterations, gadolinium-enhancements or cortical lesions), with MRI amelioration correlating with clinical NP improvement during follow-up in three studies (27,37,42). In two cases, MRI lesion load stability was considered as a surrogate positive biomarker (43,44). Partial or complete recovery of MRI findings was demonstrated in less than 50% of cases of NP syndromes improvement (22,43,45). In myelopathies, spinal cord MRI repeated through follow-up yielded inconsistent correlation with the clinical response: MRI lesions persisted in patients lacking in response to treatment (41), while reduction/disappearance of lesions was not always positively related to the clinical gain of function (34,36,40,41).

Analysing quantitative brain MRI techniques, magnetization transfer imaging (MTI) was assessed in 3 studies (51–53). At white matter (WM) level, changes across follow-up in mean magnetization transfer ratio - histogram peak height (MTR-HPH) positively correlated with clinical improvement of patients with active NPSLE manifestations at the baseline visit (51). Cerebral metabolites ratios, instead, measured using magnetic resonance spectroscopy (MRS), were assessed in 5 studies (46–48,50,54): N-acetylaspartate/Creatine (NAA/Cr) ratio measured with single-voxel MRS increased following successful clinical management of NPSLE.

Other neuroimaging techniques evaluated included brain computed tomography (CT) in a single study (55), single-photon emission computed tomography (SPECT) in 6 (22,25,33,43,56,57) and positron emission tomography (PET) in 2 (22,58) studies. In particular, SPECT was used to monitor treatment response, and, when the baseline scan was altered, it showed increased cerebral blood flow following clinical improvement (22,25,43,56,57).

Neurophysiology outcome measurement instruments included electroencephalography (EEG), evoked potentials (EPs), electromyography (EMG). EEG was evaluated in 4 studies (27,35,59,60): quantitative EEG improvement during follow-up (59) was in line with clinical improvement of different major NP events (5 out of 6 patients). In a RCT (27) 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 (27). Stojanovich et al. (60), 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.

Domain - 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 (5 studies) and British Isles Lupus Assessment Group index (BILAG) (4 studies). In five of these studies, the

above-mentioned indices were used to monitor NP manifestations response following a specific treatment (RTX) (22–24,26,43). A retrospective study has shown ECLAM score reduction after prompt treatment for severe NPSLE (42), 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 (59,62). The global status of disease activity (e.g. high/moderate/low disease activity or remission) was not assessed in the studies evaluated in this SLR.

Domain - relapse

Different NP syndromes were evaluated for relapses, mainly in observational studies. LM (11 studies), psychosis and seizures (8 studies) were the manifestations most frequently assessed. SELENA Flare Index (SFI) measured NPSLE relapses in a cohort study of patients treated with RTX (23). Considering specific NP syndromes, 22 studies assessed relapses applying its own definition each (Table 3). B-cells levels after RTX therapy correlated with moderate flares (24), while a SLR highlighted a strong correlation between anti-phospholipid antibodies (aPL) positivity and the overall risk of NP syndromes relapse (63).

Domain - damage

Quantification of global damage was also measured, specifically through Systemic Lupus International Collaborating Clinics (SLICC) ACR Damage Index (SDI), in 6 studies (23,27,35,61,62,64).

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 physician perception of patients’ disease activity and neurological function. 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 (10,65–74). Simplified 4-points (75) and 5-points scales (76) were also used. Neuwelt's criteria, based on the combination of clinical data and anatomic imaging, were introduced (77,78) to define clinical outcomes of severe NPSLE patients after CYC therapy and were assessed in 6 studies (389 patients). This set of criteria included three (improved, stabilized and progressed)(45,77–79) or two groups (responders and non-responders)(33). In detail, the different conditions were defined as follows: improved status in

presence of sustained complete clinical recovery and stabilized or improved findings on anatomic imaging studies; stabilized status for no new clinical or imaging abnormalities without modification of previous abnormalities; progressed NP status when old NP symptoms exacerbated, or new ones developed during follow up. Barile-Fabris et al. (27) 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 37 studies for a total of 1,409 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 1,104.9 (1,436 days)).

Domains - Glasgow Coma Scale, PtGA, fatigue and function

Glasgow Coma Scale (GCS), a neurological scale which records the state of consciousness, was assessed in an open-label study including 5 patients suffering from acute confusional state to monitor RTX response (22). Considering Patient Global Activity (PtGA), 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 (80), while a 7-points scale was adopted in a RCT to quantify symptoms severity (28). Regarding fatigue, the Fatigue Severity Scale (FSS) and the Modified Multidimensional Assessment of Fatigue (MAF) Questionnaire were evaluated in a longitudinal study (80), in which a correlation between fatigue impact on daily life and cognitive impairment was found, the Krupp Fatigue Inventory was adopted in a RCT assessing the role of memantine in cognitive impairment due to SLE (81). 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 of 33 patients with variable NP syndromes (82). The Medical Outcome Study Short Form 36 (SF-36) was administered to 4,999 heterogeneous NPSLE patients in 15 studies (1 SLR, 1 cross-sectional and 13 longitudinal studies)(10,25,62,65–73,75,83,84).

Domain - hospitalization

Hospitalization was assessed in 3 observational studies (24,85,86), of which two with retrospective design. These studies considered the rate of re-admission to hospital related to neurological relapse as a measure of outcome for NPSLE (85), the duration of the hospitalization (86) and hospitalizations due to adverse events of SLE treatments (24).

Core area – Death/lifespan

Domain mortality

Twenty-two studies addressed death/mortality as appropriate OMIs. Mortality was assessed as related to NP manifestations per se (87,88), or to administered treatments (77,78). Moritani et al. described an association between mortality and brain diffusion-weighted imaging MRI patterns corresponding to vasogenic oedema (38).

Contextual factors

Domain - adverse events

Adverse events (AEs) and side effects of therapies administered for NPSLE were recorded in 16 studies. The most frequent types of AEs recorded were severe infections, or specific drugs-related AEs (e.g. hypertension, Cushingoid features, alopecia, neoplasms)(22,27,49,77,89).

Domain - glucocorticoid therapy

Finally, GCs dosage reduction was investigated as an 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 (23,43). The corticosteroid-sparing effect of CYC versus methylprednisolone pulses was demonstrated after 6 and 15 months in a RCT (27).

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 (2,10,90). To the best of our knowledge, this SLR represents 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 (17), 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 (15).

To this end, the systematic assessment of outcome measures used in NPSLE has not been addressed so far. 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, with most of the evidence derived from observational

studies. Going deeply into the significance of single OMIs, the most frequently assessed were PhGA (37 studies), conventional brain or spinal cord MRI, death/mortality, NP symptoms recurrence (22 studies each), and AEs (16). However, characterization of PhGA or recurrence was not homogeneous, and some studies did not report exact definitions (28,34,91,92). Some studies adopted Likert scales or Neuwelt's criteria, but stratification of patients according to these tools was not univocal (66,75,76). Regarding MRI, few studies specifically addressed the significance of elementary lesions (37), 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 (46,51). Nevertheless, low-rate clinical application, as well as the absence of standardization and homogenization in data analysis, claim for further validation of such procedures (93). In SPECT studies (22,25,33,43,56,57), the mean number of patients included was low (24.2, SD 9.2), similarly to other neuroimaging or neurophysiological studies. Indexes referring to disease activity measures (e.g. SLEDAI) were mainly used in longitudinal studies including other non-NPSLE patients (23–26), 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 (65,75) from the patient's point of view.

Given this large heterogeneity, there is the claim to prioritize NPSLE domains according to OMERACT frameworks in order to define a core domain set, and finally apply, to each outcome measure included, the concepts of truth, discrimination and feasibility, the main properties that need to be addressed to validate an instrument and to include it in clinical trials (15). Moreover, due to the multifaceted character of NPSLE involvement, our work revealed a lack of outcome measures used crosswise, both globally and/or specifically in neuro lupus "as a whole" (94). From this perspective, the question is whether it is time to approach the individual NP manifestations by adopting instruments validated in other disciplinary contexts (e.g. neurology, rehabilitation, psychiatry) and for specific manifestations. The trajectory for individual entity, passing through the proper diagnosis and attribution, could foresee a dedicated outcome measure for single conditions, conceptualized in pathophysiological or prevalence terms.

This study has some limitations, for example it was out of the scope of this SLR the characterization of specific properties of OMIs (truth, feasibility and discrimination) (15,19), and this aspect should be investigated in the 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 (10).

In conclusion, our study revealed a significant 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 (83 included articles).

Variables	Frequency	
Number of studies, N (%)	All studies	83 (100%)
	RCT	3 (3.6%)
	SLR/meta-analysis	5 (6.0%)
	Cohort study	33 (39.8%)
	Other observational	42 (50.6%)
Number of participants, N (mean±SD)	All studies	15,974 (194.8±895.9)
	RCTs	93 (31.0±20.5)
	SRL/meta-analysis	8,056 (2,014±3,990.7)
	Cohort study	6,337 (192.0±293.7)
	Other observational	1,488 (35.4±44.9)
Mean age, years (±SD)		35.2±6.0
Female, mean percentage		89.9
Mean disease duration, years (±SD)		5.4±2.8
Mean follow up, months (±SD)		956.2±1,221.1
NPSLE manifestations, N of studies (%)	Aseptic meningitis	21 (25%)
	Cerebrovascular disease	40 (48.1%)
	Demyelinating syndrome	20 (24.1%)
	Headache	39 (47.0%)
	Movement disorders	23 (27.7%)
	Myelopathies	38 (45.8%)
	Seizure disorders	44 (53.0%)
	Acute confusional state	32 (38.5%)
	Anxiety disorders	20 (24.1%)
	Cognitive dysfunction	33 (39.8%)
	Mood disorders	41 (49.4%)
	Psychosis	41 (49.4%)
	Acute inflammatory polyradiculoneuropathy	8 (9.6%)
	Autonomic disorder	10 (12.0%)
	Mononeuropathy	26 (31.3%)
	Myasthenia gravis	9 (10.8%)
	Cranial neuropathy	33 (39.7%)
	Plexopathy	7 (8.4%)
	Polyneuropathy	30 (36.1%)
	Others	6 (7.2%)

List of abbrevations: RCTs, Randomized clinical trials; 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 (17), reported in the 83 selected articles.

Concepts	Core Areas	Domains	Instruments	N. of Studies Using the Instrument	Ref.
Pathophysiology	**Manifestations / Abnormalities**	**Laboratory markers**	• Complement levels	7	(22–28)
			• Anti-dsDNA	4	(23–25,28)
			• Anti-NMO IgG	1	(29)
			• Immunoglobulins (IgM, IgA, IgM) levels	1	(24)
			• Lymphocytotoxic antibodies	1	(28)
			• Anti-neuronal antibodies	1	(28)
			• Peripheral blood B cell subsets	2	(24,25)
			• Expression of functional molecules on CD4-positive cells (CD40L, ICOS; CD69, CD4)	1	(22)
			• PBMCs CD40-expressing and CD80-expressing CD19-positive cells, CD20-positive cells	2	(22,25)
			• Total leukocytes/lymphocytes count	1	(27)
			• CSF Interleukin (IL)-6 level	1	(22)
			• CSF IgG Index	1	(22)
			• CSF GFAP level	1	(30)
			• CSF NFL	1	(30)
			• CSF OPN	1	(31)
		Instrumental markers	• Fundoscopy	1	(89)
			• Field test	1	(89)
			• Electrophysiological studies (EMG)	4	(27,35,60,95)
			• EEG	4	(27,35,59,60)
			• Evoked Potentials	3	(27,35,60)
			• Brain computed tomography	1	(55)
			• Brain/spinal cord MRI	22	(22,25,27,32–50)
			• MTR-HPH	3	(51–53)
			• MRS	5	(46–48,50,54)
			• SPECT	6	(22,25,33,43,56,57)
			• 18FDG-PET	2	(22,58)
		Cognitive field	• ACR-SLE battery	2	(80,81)
			• MMSE	3	(35,81,96)
			• HDS-R	1	(43)
			• Cognitive Failures Questionnaire	1	(80)
			• Wechsler Adult Intelligence Scale	1	(52)
			• ANAM	1	(81)
			• Cognitive reassessment battery	1	(28)
		Sensory-motor field	• ASIA Impairment Scale	2	(97,98)
		Depression/Anxiety field	• CES-D	1	(80)
			• HAM-D	4	(35,43,62,96)
			• HAM-A	1	(62)
			• HADS	1	(52)
			• Calgary Depression Scale	1	(81)

			• Profile of Mood States	1	(28)
		Psychiatric field	• BPRS	4	(22,35,43,96)
			• YMRS	1	(43)
		Pain	• The Short-Form McGill Pain Questionnaire	1	(80)
		Disease activity	• SLEDAI-2K	4	(25,33,64,69)
			• SLEDAI	13	(22,25,27,35,42,43,46–48,54,59,61,82)
			• SELENA-SLEDAI	5	(23,25,26,62,81)
			• ECLAM	2	(42,61)
			• BILAG	4	(24,25,43,97)
		Relapse	• SFI	1	(23)
			• Own definition	22	(10,23–26,35,40,45,60,62,63,71–73,91,95,97–102)
		Damage	• SDI	6	(23,27,35,61,62,64)
Impact	**Life impact**	**PhGA**	• Likert scale (7-, 5- or 4-points scale)	13	(10,65–76)
			• Neuwelt's response criteria	6	(27,33,45,77–79)
			• Clinical response (own definition)	37	(22,23,25,26,28,32,34–38,40–44,49,51,53,55,58,60–62,64,83,86,91,92,96,98–101,103–105)
		GCS	• GCS	1	(22)
		PtGA	• Patient's Assessment of Own Functioning Inventory	1	(80)
			• Patient's Assessment of Symptom (7-poins scale)	1	(28)
		Fatigue	• FSS	1	(80)
			• MAF	1	(80)
			• Krupp Fatigue Inventory	1	(81)
		Function	• EDMUS-GS	2	(36,98)
			• EDSS	2	(29,52)
			• modified Rankin Scale	2	(75,95)
			• Walking Index for Spinal Cord Injury	1	(97)
			• Visual acuity	2	(27,89)
		Quality of life	• SF-36	15	(10,25,62,65–73,75,83,84)
			• EuroQol-5D questionnaire	1	(82)
		Hospitalization	• Number	3	(24,85,86)
	Death/Lifespan	**Mortality**	• Death, mortality, mortality rate	22	(10,23–26,29,35,38,64,71,77–79,85–88,91,96,99,100,106)
	Societal / Resource use	**-**	-	0	-
Contextual factors		**Adverse events**	• General	16	(22,23,25–28,35,42,43,49,60,77,78,81,89,97)
		Glucocorticoid therapy	• Minimal dose, GC reduction	7	(23,25–27,35,43,64)

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; NFL, neurofilament triplet protein; OPN, osteopontin; 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; PtGA, 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; ANAM, Automated Neuropsychological Assessment Metrics; 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	(23)
Exacerbations of NP syndromes	2	(91,97)
Recurrent or new NP events	6	(10,26,45,71–73)
Psychotic flare	1	(101)
Relapse of symptoms	6	(25,40,60,95,99,100)
Relapse of symptoms confirmed by MRI	1	(98)
Recurrent NPSLE	1	(63)
Flares defined as a new BILAG grade A (not present at baseline), or a new grade B	1	(24)
Number of seizures per month	1	(35)
SLE flare	3	(25,62,102)

List of abbreviations: NP, neuro-psychiatric; SLR, systematic literature review; SFI, SELENA-SLEDAI Flare Index; MRI, magnetic resonance imaging; SLE, Systemic Lupus erythematosus; BILAG, British Isles Lupus Assessment Group index.

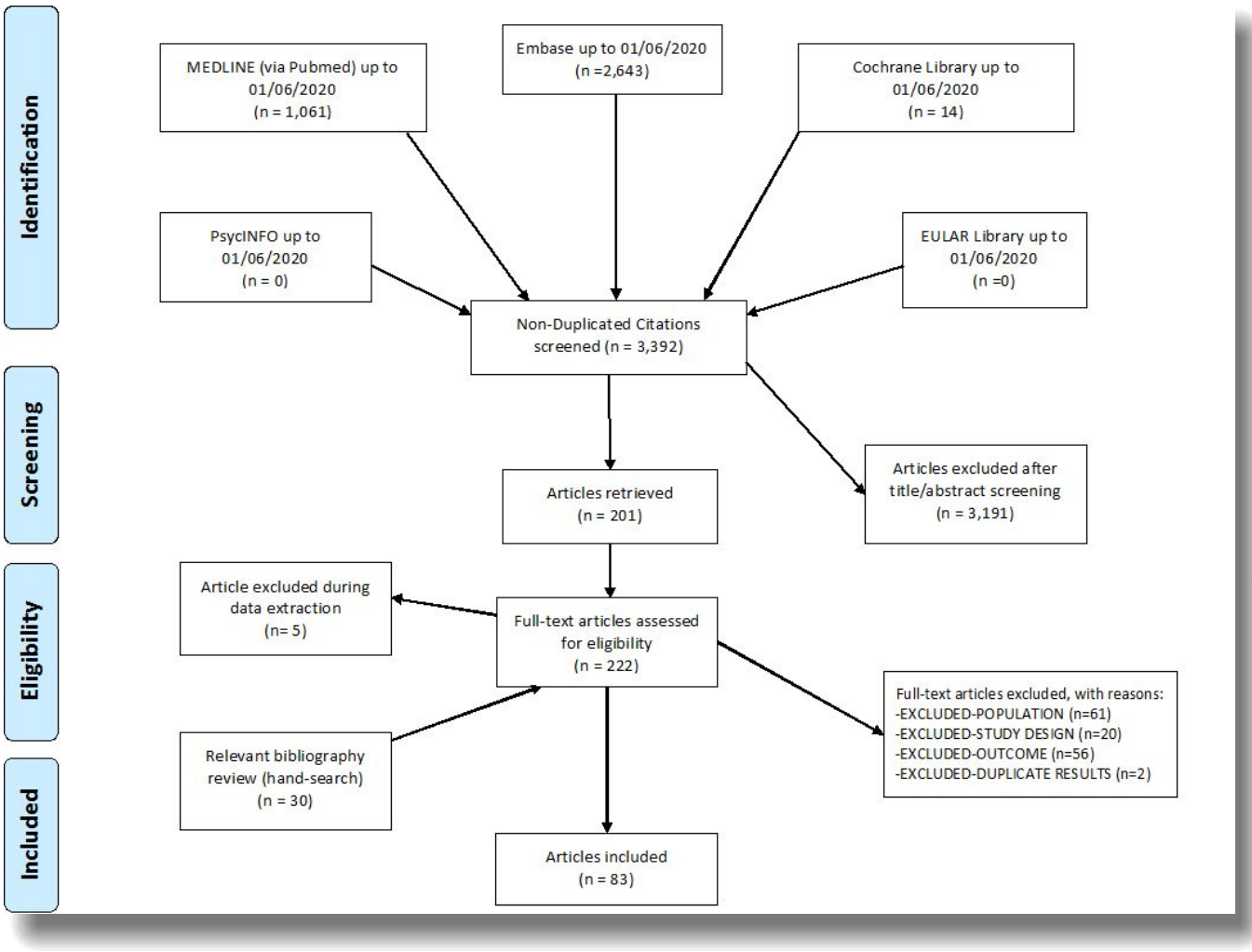
Table 4. Specific definitions for physician global assessment for NPSLE, according to studies retrieved in the SLR.

Definition of physician global assessment for NPSLE	N° of studies	Ref.
Likert scale (7-, 5- or 4-points scale)	13	(10,65–76)
Neuwelt's response criteria	6	(27,33,45,77–79)
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	(32)
Active/inactive NPSLE	1	(55)
Generic description of symptoms improvement	1	(40)
Generic description of response to treatment	2	(34,91)
Symptoms resolution	1	(92)
Motor, sensory and sphincter recovery	1	(49)
Arbitrary 3-level categorical outcome as improved, stable, or worse	1	(103)
Improvement of symptoms and presence of any neurologic sequelae	1	(64)
Psychosis remission	1	(101)
Complete/partial resolution of symptoms, absence of improvement	3	(36,41,98)
Complete resolution of symptoms, improvement, no change, worsening	1	(58)
Symptoms improved/stable/worsened	1	(44)
Recovery from neurologic symptoms	1	(86)
Resolution, improvement, stability of symptoms AND neurological examination	1	(38)
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	(104)
Symptoms present/ameliorated/worsened/absent	1	(61)
Improvement through clinical appraisal	2	(35,96)
Presence/absence of new seizures	1	(105)
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	(37)
“Improved” status: at least 50% recovery of signs and/or Symptoms; “no response”: less than 50% recovery; “worse”: progression of the condition.	1	(83)
Presence of major refractory and persistently active events	1	(42)
Improvement in clinical condition established by both the patient and the doctor	1	(60)

Change in clinical NP status defined as worse, stable, or improved by multidisciplinary consensus	2	(51,53)
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	(43)
Neurological examination to define functional response	2	(26,99)
Improvement in symptoms and consciousness state	1	(22)
Patient survived, expired, relapsed	1	(100)
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	(23)
Definition not explicated	3	(25,28,62)

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 (17) to NPSLE.