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EULAR Sjogren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjogren's syndrome

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Abstract Objective

To develop a disease activity index for patients with primary Sjögren's syndrome (SS): the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI).

Methods

Thirty-nine SS experts participated in an international collaboration, promoted by EULAR, to develop the ESSDAI. Experts identified 12 organ-specific "domains" contributing to disease activity. For each domain, features of disease activity were classified in 3 or 4 levels according to their severity. Data abstracted from 96 patients with systemic complications of primary SS were used to generate 702 realistic vignettes for which all possible systemic complications were represented. Using the 0–10 physician global assessment (PhGA) scale, each expert scored the disease activity of 5 patient profiles and 20 realistic vignettes. Multiple regression modelling, with PhGA used as the dependent variable, was used to estimate the weight of each domain.

Results

All 12 domains were significantly associated with disease activity in the multivariate model, domain weights ranged from 1 to 6. The ESSDAI scores varied from 2 to 47 and were significantly correlated with PhGA for both real patient profiles and realistic vignettes ($r=0.61$ and $r=0.58$, respectively, $p<0.0001$). Compared to 57 (59.4%) of the real patient profiles, 468 (66.7%) of the realistic vignettes were considered likely or very likely to be true.

Conclusion

The ESSDAI is a clinical index designed to measure disease activity in patients with primary SS. Once validated, such a standardized evaluation of primary SS should facilitate clinical research and should be helpful as an outcome measure in clinical trials.

Author Keywords primary Sjogren's syndrome ; outcome assessment ; systemic features ; activity index ; clinical vignettes ; disease activity

Primary Sjögren's syndrome (SS) is a systemic disorder characterized by lymphocytic infiltration and progressive destruction of exocrine glands. The inflammatory process can, however, affect any organ. As a result, clinical features can be divided into two facets: (i) benign but disabling manifestations such as dryness, pain and fatigue, affecting almost all patients; and (ii) severe systemic manifestations that affect 20% to 40% of patients.

Evidence-based therapy for SS is largely limited to treatments that improve sicca features.[1] Clinical trials of disease-modifying therapies have used a variety of ad hoc outcome measures mainly based on glandular features or patient symptoms, but not systemic features.[2–6] Valid activity indexes are needed [7–9] to assess the effectiveness of new targeted therapies, such as B-cell targeted

therapies that have shown promising results for both severe systemic [10 , 11] and glandular features.[12 –15] Two disease activity indexes have recently been proposed: the SS disease activity index (SSDAI) [16] and the Sjögren's Systemic Clinical Activity Index (SCAI).[17] The development of these indexes was based on exploratory studies conducted in single countries, but they serve as the basis of the present collaborative project. Thus, the European League Against Rheumatism (EULAR) has promoted an international collaboration to develop consensus disease activity indexes. Two indices are currently in development: (i) a patient-administered questionnaire to assess patient symptoms, the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI); and (ii) a systemic activity index to assess systemic complications, the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI).

We now describe the development and initial validation of the ESSDAI. This index was developed with the help of a worldwide panel of primary SS experts using physician global assessment (PhGA) of disease activity as an external criterion. The aim is for the ESSDAI to be used as outcome criteria to evaluate primary SS in a standardized way in both clinical trials and daily practice.

METHODS

This paper results from a collaboration of experts identified through their involvement in the primary SS field, headed by a steering committee of 7 physician experts in SS (HB, SB, JEG, XM, ET, AT, CV), a clinical epidemiologist (PR) and a rheumatologist, a fellow in clinical epidemiology (RS). The research protocol was endorsed by EULAR (project code CLI 010).

The steps of the development of the ESSDAI are summarized below; the entire methodology is available online (Appendix 1).

Selection of relevant domains and definition of items

Domains of organ-specific involvement relevant to assess disease activity were selected in these steps. For each domain, the different clinical manifestations were ranked by level of activity (i.e., items). For selection of domains relevant to disease activity and definition of items for each domain, steering committee members prepared a preliminary proposal on the basis of their clinical experience, literature review and previous work.[16 , 17] The preliminary selection of domains and items were successively submitted to the expert panel. Experts had to rate the importance of each domain or suggest any additional domains or changes to proposed items. Intention-to-treat was used as a help for experts to define the different activity levels that ranged from no activity (requiring no treatment) to high activity (requiring high dose steroids or immunosuppressant). The experts' proposals were analyzed, then discussed and voted on during a meeting.

Elaboration of clinical vignettes

In this step, realistic clinical vignettes were generated from real patient profiles.

Abstraction and standardization of real patient profiles

Five members of the steering committee supplied 96 profiles of their patients with systemic complications of primary SS. Each profile had to contain sections on "History" (demographic data and past medical history), "Today" (clinical symptoms and results of imaging examination) and "Laboratory" (biological features). Patient profiles included data from the baseline and 2 follow-up visits (3 and 6 months).

Abstraction of descriptions of items from real patient profiles

From patient profiles, 96 histories and 364 items, included in the "Today" and "Laboratory" sections, were extracted and standardized by the same investigator (RS). Description of all ESSDAI items were obtained and entered in a database with their corresponding scoring (domain and activity level). Each item had a median of 8.5 (interquartile range [IQR: 4–15] descriptions).

Generation of realistic clinical vignettes

Determination of construction rules

Data from primary SS patient cohorts of 5 members of the steering committee (SB, XM, ET, AT, CV)[16 –20] were used to construct a sample of vignettes with characteristics similar to European patient cohorts.

Generation of clinical vignettes

In total, 720 clinical vignettes were generated by a combination of "History" and items from the "Today" and "Laboratory" sections, with respect to the domain and item distribution defined previously. However, because items in the database referred to only systemic features, descriptors of symptoms such as dryness, pain and fatigue were generated and assigned to 30% of the patient vignettes.

Assessment

The 96 real patient profiles and the 720 clinical vignettes were randomly assigned to the 40 experts. Each expert had to rate 5 real patient profiles (rated by 2 raters each) and 20 clinical vignettes (18 were "unique" and 2 were "common" to 2 raters). For the survey, an

internet-secure relational database was constructed. Patient data were presented chronologically, and the responses could not be changed. For all visits of each profile or vignette, experts had to assess disease activity by use of the PhGA on a 0–10 numerical scale and a 5-point scale (inactive, low, moderate, high, very high activity). For the first visit of each profile or vignette, they also had to evaluate the plausibility of each patient case with use of a 5-point scale (very unlikely, unlikely, possible, likely, very likely) by answering the following question: “Please indicate, according to your clinical experience and knowledge of the disease, the likelihood that this patient scenario is a real case”.

Statistical methods

Determination of domain weights and construction of the ESSDAI

Realistic clinical vignettes were used to determine domain weights. Disease activity assessed by the PhGA was used as an external criterion. Bivariate analysis involved Pearson’s correlation between PhGA and each domain separately; for each domain, scores ranged from 0 = “no activity” to 3 = “high activity”. All domains were entered into multivariate models; the PhGA was used as a dependant variable and each domain was an explanatory variable. Two models were evaluated: a multiple linear regression model and a robust regression model with the least-median-of-squares method with an MM estimator.[21 , 22] The weights assigned to each domain were derived from the regression coefficients of the multivariate model and rounded to form simplified indices. The weight of each item was obtained by multiplying the weight of the domain by the level of activity.

Preliminary validation

The ESSDAI was then calculated for all real patient profiles and realistic clinical vignettes. Construct validity was assessed by the strength of correlation between the ESSDAI score and the disease activity score assigned by the expert.

Sensitivity analyses

To evaluate the stability/robustness of the domain weight estimation, other models were tested: a logistic regression model with the 5-point scale used as an external criterion and different multiple linear regression models after pooling items that clustered.

Patient profile plausibility

Evaluation of patient profile plausibility of realistic clinical vignettes was compared to that of real patient profiles by a Cochran-Armitage trend test.

Reliability of disease activity scoring

The evaluation of clinical vignettes common to 2 raters was used to assess inter-rater reliability:

- For the 0–10 PhGA: intraclass correlation coefficient (ICC) and Bland and Altman graphical analysis[23 , 24]
- For the 5-point scale: global agreement and Kappa statistics[25 , 26]

The evaluation of real patient profiles was used to assess intra-rater reliability by the ICC, if at the first follow-up visit, the physician considered the disease activity unchanged. ICC confidence intervals were estimated with bootstrapping methods, with 1000 replications.[27]

For all statistical analyses, a p-value less than 0.05 was considered statistically significant. All statistical analyses involved use of SAS release 9.1 and R release 2.2.1 statistical software packages.

RESULTS

Characteristics of expert panel

Of 40 invited primary SS experts, 39 took part in the study (35 Europeans from 13 countries and 4 North Americans). The median age of experts was 49 [IQR: 46–58] years; 35 were rheumatologists, 3 were internists and 1 was an oral medicine practitioner. All but 2 (94.9%) had ≥ 10 years of experience in managing primary SS. All were involved in clinical research, and 23 (59.0%) were also involved in basic science research into primary SS.

Selection of domains and definition of items

All 10 domains (constitutional and lymphadenopathy, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral nervous system, central nervous system, hematological) proposed by the steering committee were included. Experts decided to divide the “

constitutional and lymphadenopathy" domain into 2 domains and to add a biological domain but not add a hepatic domain (considered to result from damage). The definition of the different activity levels (items) of each domain was obtained by consensus after discussion during meetings of the steering committee and experts.

Characteristics of real patient profiles and realistic vignettes

Thirty-nine of the 40 experts completed the rating of the 96 real patient profiles and 702 of the 720 clinical vignettes (Table 1). Real patient profiles, selected for the extent of systemic involvement, had a significantly higher number of involved organs than did realistic clinical vignettes (2.83 ± 1.46 vs. 2.14 ± 1.08 ; $p < 0.0001$).

Determination of domain weights and derivation of the ESSDAI

All domains, except haematological, glandular, articular and biological domains, showed a significant positive correlation with PhGA score (Table 2). All domains were entered in 2 multivariate regression models. Multiple linear and least-median-of-squares regression models provided similar results ($R^2 = 0.29$ and $R^2 = 0.30$, respectively). In both models, all domains were significantly associated with disease activity (PhGA), and the weight estimation was similar. The weights derived from the regression coefficients were rounded to obtain a simple index (Tables 2 and 3).

Preliminary validation of the ESSDAI in real patient profiles and realistic vignettes

The mean ESSDAI scores were 15.48 ± 9.16 and 9.04 ± 6.43 for real patient profiles and realistic vignettes, respectively. ESSDAI scores were significantly correlated with the PhGA score ($r = 0.58$ for realistic vignettes and $r = 0.61$ for real patient profiles, $p < 0.0001$; Figure 1). The maximum theoretical ESSDAI score is 123; however, only 25% of realistic vignettes and the real patient profiles had a score ≥ 13 and ≥ 21 , respectively. The highest score was 42 and 47 for the realistic vignettes and real profiles, respectively (Figure 1).

Sensitivity analyses

Other models for testing sensitivity analyses led to similar domain weights and similar correlation with the PhGA score.

Patient profile plausibility

Overall, experts considered 468 (66.7%) of the 702 vignettes likely or very likely to be true, as compared with 57 (59.4%) of the 96 real patient profiles ($p = 0.09$).

Reliability of disease activity scoring

Inter-rater reliability assessed by the ICC on 76 common vignettes was 0.41 [0.18–0.60] for the PhGA. Bland and Altman graphical analysis revealed no systematic errors (mean difference = -0.16) but a variability of rating among experts (95% agreement interval [-4.92 to $+4.61$]). The ratings of the same vignette by 2 different experts differed by ≤ 1 point for 37 vignettes (48.7%), by 2 to 3 points for 30 (39.5%), and by > 3 points for 9 (11.8%). The weighted Kappa statistic for disease activity rating by the 5-point scale was 0.32 [0.18–0.47]. When grouping the highest activity scores (high and very high activity) and the lowest scores (inactive, low and moderate activity), the observed agreement was 72.4% and the Kappa coefficient 0.42 [0.21–0.63].

Intra-rater reliability of the PhGA for 20 real patient profiles with unchanged activity at the first follow-up visit as assessed with the ICC was 0.86 [0.68–0.94].

DISCUSSION

The ESSDAI is a consensus clinical index designed to measure disease activity in patients with systemic complications of primary SS. This index is modelled on physician's judgment of disease activity. It results from a large collaboration of European and North American experts in primary SS. Compared to the PhGA, the ESSDAI performed satisfactorily for evaluation of disease activity in primary SS.

In the absence of an available "gold standard" or true understanding of disease process, the most accurate and meaningful method of disease activity assessment is to attempt to model the physician judgment. But any scale quantifying physician judgment of disease activity is a simplification of a complex mental process. For that purpose, 2 main gold standards have been used in the development of disease activity indexes: (i) the PhGA [28–30] and (ii) the intention-to-treat approach.[31, 32] The PhGA was used for the development of the systemic lupus disease activity index (SLEDAI) in systemic lupus erythematosus (SLE),[28–30] whereas the intention-to-treat approach was used for the development of the British Isles lupus assessment group (BILAG) for SLE [31] and the disease activity score (DAS) for rheumatoid arthritis (RA).[32] However, unlike RA that quasi-exclusively affects articular system and where therapeutic decision is reproducible, the multisystemic nature of primary SS make therapeutic decision more variable. In addition, evidence-based therapeutic management of SLE is currently more advanced than in primary SS. Moreover, in the BILAG, this approach was used to define, in each domain, the different classes (A, B, C, D, E) and not as "gold standard" to determine domain weights. Therefore, in the absence of effective

treatment or consensual therapeutic management and because of the variability of physician habits, the intention-to-treat approach might be more difficult to apply as a gold standard for primary SS at this time.

In addition, the extent to which each organ involvement or patient symptoms of fatigue and pain can influence the physician's evaluation of disease activity, in such a polymorphous disease, is extremely variable, as demonstrated by the limited reliability of the PhGA. These discrepancies among physicians' views, even among disease experts, justify the necessity for a more objective and standardized scoring system to homogenise assessment of disease activity in different settings, by different physicians, experts but also less experienced physicians. Similar to correlation of SCAI scores with the PhGA, [17] that of ESSDAI scores with the PhGA was about 0.60. These correlations were lower than that from other studies evaluating disease activity scores for various systemic disorders [16 , 29 , 33]. However, in most of these studies, the experts involved were trained to the rating of the PhGA and the different activity tools to improve reliability and homogeneity of this scoring. In the present study, to be closer to usual practice, we decided not to perform a training exercise.

The ESSDAI was developed by a large panel of primary SS experts and attempted to reflect their thought process. This may have ensured the content validity of the ESSDAI, including all relevant determinants of disease activity. The validity of the ESSDAI was further confirmed by the significant association of all domains with disease activity in our model. Previous primary SS activity indexes have been developed with use of cohorts in which about half of the patients had inactive or weakly active disease.[16 , 17] Our strategy was to use data from selected patients with systemic features to generate realistic clinical vignettes. This methodology enabled us to obtain a large number of vignettes (more than would have been possible with real patients) representing all possible systemic disease involvement (i.e., items). We then evaluated the extent to which each item influenced the evaluation of disease activity, which had not been possible in previous studies that did not include all organ-specific features.[16 , 17] As in all global scoring system,[16 , 29] similar ESSDAI scores (same disease activity) may reflect different domains involved. As a further component of this project we will also be evaluating the most common patient-reported symptoms such as dryness, pain and fatigue in a patient-completed questionnaire the ESSPRI.

A major challenge in designing a systemic index is distinguishing between damage and disease activity. The most frequent approach, to avoid scoring damage, is to consider manifestations as active only if "new" or "worsening." Under these scoring systems, when patients are evaluated at two time points, a persistent manifestation will not be rated at the second time point, which may cause an erroneous interpretation of improvement even though the patient's condition has not changed. To avoid this, all ESSDAI items were defined without reference to a previous assessment, but with an advice not to rate as active stable long-lasting features related to damage.

The ESSDAI is a systemic disease activity index developed to allow a standardized evaluation of disease activity in primary SS patients. Further studies are needed to assess the reliability and sensitivity to change of the ESSDAI. Once validated, if uniformly applied, the ESSDAI might enable comparison between studies and facilitate clinical research into primary SS. After the development of the patient-completed questionnaire (ESSPRI), the use of both the ESSDAI and ESSPRI for outcome assessment in randomized controlled trials should allow for assessing all facets of the disease.

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ABBREVIATIONS

BILAG : British Isles Lupus Assessment Group
 DAS : Disease Activity Score
 ESSDAI : EULAR Sjögren's Syndrome Disease Activity Index
 ESSPRI : EULAR Sjögren's Syndrome Patients Reported Index
 EULAR : European League Against Rheumatism
 ICC : Intraclass Correlation Coefficient
 PhGA : Physician Global Assessment
 ROC : Receiver Operating Characteristic
 SCAI : Systemic Sjögren's Syndrome Clinical Activity
 SLE : Systemic Lupus Erythematosus
 SLEDAI : Systemic Lupus Disease Activity Index
 SS : Sjögren's Syndrome
 SSDAI : Sjögren's Syndrome Disease Activity Index

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Figure 1

Distribution of ESSDAI scores and correlation with disease activity in real patient profiles and realistic vignettes

Figures 2A, 2B, 2C refer to the 702 realistic clinical vignettes, and figures 2D, 2E, 2F refer to the 96 real patient profiles. Distribution of ESSDAI scores in realistic vignettes (A) and real patient profiles (D), ESSDAI score for each level of global activity as defined by physicians on the 5-point scale (B and E), and correlation between ESSDAI scores and physicians' ratings of disease activity by the physician global assessment (PhGA) scale (0–10 scale) (C and F). For box plots of ESSDAI scores, the boxes represent the 25th and 75th percentiles; the lines within the box represent the median; the dot inside the box, linked by a line, represents the mean; and the whiskers extend to the most extreme data point, which is no more than 1.5 times the interquartile range (difference between the 75th and 25th percentiles) from the box. Values that are more extreme were considered outliers and are plotted individually (dots).

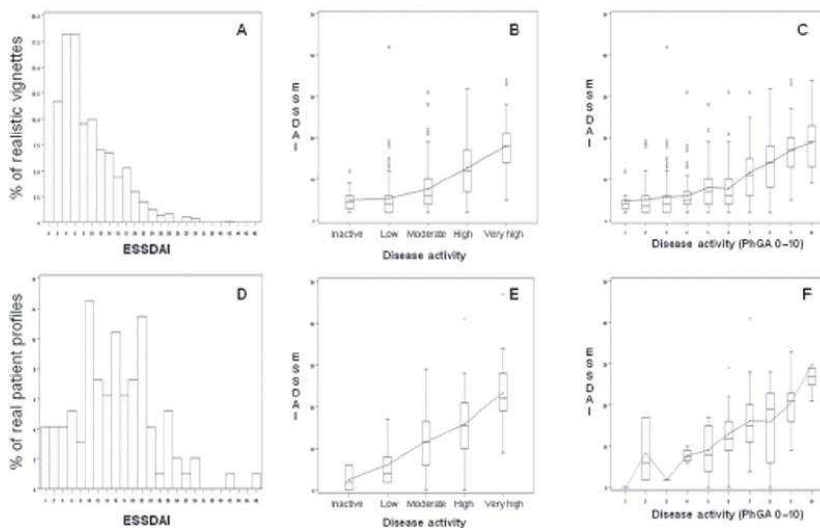


Table 1

Demographic characteristics for the 96 real patient profiles and 702 realistic clinical vignettes.

| | Real patient profiles (n=96) | Realistic clinical vignettes (n=702) |
|--|------------------------------|--------------------------------------|
| Age | 55.92±15.13 | 55.85±14.21 |
| Female sex | 89 (92.71%) | 647 (92.17%) |
| Disease duration | 8.58±7.25 | 8.46±7.04 |
| Oral dryness | 90 (93.75%) | 641 (91.31%) |
| Ocular dryness | 82 (85.42%) | 599/697 (85.94%) |
| Objectively assessed dryness | 63/63(100%) | 456/456 (100%) |
| Anti-SSA antibodies | 82 (86.42%) | 595 (84.76%) |
| Anti-SSB antibodies | 56 (58.33%) | 399 (56.84%) |
| Lymphocytic sialadenitis with focus score ≥1 | 70/74 (94.59%) | 490/525 (93.33%) |
| Organ involvement | | |
| Constitutional symptoms | 14 (14.58%) | 76 (10.83%) |
| Lymphadenopathy | 9 (9.38%) | 80 (11.40%) |
| Lymphoma | 8 (8.33%) | 35 (4.99%) |
| Glandular | 27 (28.12%) | 270 (38.46%) |
| Articular | 36 (37.5%) | 396 (56.14%) |
| Cutaneous | 29 (30.21%) | 74 (10.54%) |
| Pulmonary | 22 (22.92%) | 90 (12.82%) |
| Renal | 14 (14.58%) | 37 (5.27%) |
| Muscular | 2 (2.08%) | 22 (3.13%) |
| Peripheral nervous system | 15 (15.62%) | 64 (9.12%) |
| Central nervous system | 7 (7.29%) | 20 (2.85%) |
| Hematological | 25 (26.04%) | 72 (10.26%) |
| Biological markers of B-cell activation | 64 (66.67%) | 268 (38.18%) |

Data are presented as number (%) or mean±SD.

Table 2

Correlation between domains and disease activity, as assessed by the physician global assessment (PhGA) scale, and regression coefficients and domain weights obtained with the least-median-of-squares robust regression model with an MM estimator.

| Domains | Bivariate analysis | | Multivariate modelling Least median of square with MM estimator | | | |
|-----------------|-----------------------|---------|---|----------------|--------|---------|
| | Correlation with PhGA | p-value | Regression coefficient | Standard error | Weight | p-value |
| Constitutional | 0.106 | 0.005 | 0.704 | 0.163 | 3 | <0.0001 |
| Lymphadenopathy | 0.134 | 0.0004 | 0.817 | 0.089 | 4 | <0.0001 |
| Glandular | 0.067 | 0.078 | 0.407 | 0.091 | 2 | <0.0001 |
| Articular | 0.063 | 0.095 | 0.489 | 0.068 | 2 | <0.0001 |
| Cutaneous | 0.156 | <0.0001 | 0.559 | 0.097 | 3 | <0.0001 |
| Pulmonary | 0.170 | <0.0001 | 1.066 | 0.115 | 5 | <0.0001 |
| Renal | 0.125 | 0.0009 | 1.090 | 0.170 | 5 | <0.0001 |
| Muscular | 0.156 | <0.0001 | 1.193 | 0.191 | 6 | <0.0001 |
| PNS | 0.197 | <0.0001 | 0.944 | 0.117 | 5 | <0.0001 |
| CNS | 0.159 | <0.0001 | 0.936 | 0.157 | 5 | <0.0001 |
| Hematological | 0.041 | 0.277 | 0.361 | 0.126 | 2 | 0.004 |
| Biological | 0.073 | 0.053 | 0.206 | 0.080 | 1 | 0.010 |

PhGA= physician global assessment; PNS= peripheral nervous system; CNS= central nervous system.

For bivariate analysis, Pearson's correlation coefficient (r) were obtained between PhGA and each domain; for each domain, scores ranged from 0 = "no activity" to 3 = "high activity". All domains were entered in multivariate regression with the least-median-of-squares model with an MM estimator. $R^2 = 0.30$ for the model. All domains were significantly associated with disease activity (as defined by the 0-10 PhGA numerical scale) in the multivariate model. The weights were derived from the regression coefficient of the multivariate model.

Table 3

The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI): Domain and item definitions and weights.

| Domain [Weight] | Activity level | Description |
|---|----------------|---|
| Constitutional [³] Exclusion of fever of infectious origin and voluntary weight loss | No = 0 | Absence of the following symptoms |
| | Low = 1 | Mild or intermittent fever (37.5°–38.5°C)/night sweats and/or involuntary weight loss of 5 to 10% of body weight |
| | Moderate = 2 | Severe fever (>38.5°C)/night sweats and/or involuntary weight loss of >10% of body weight |
| Lymphadenopathy [⁴] Exclusion of infection | No = 0 | Absence of the following features |
| | Low = 1 | Lymphadenopathy ≥ 1 cm in any nodal region or ≥ 2 cm in inguinal region |
| | Moderate = 2 | Lymphadenopathy ≥ 2 cm in any nodal region or ≥ 3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging) |
| Glandular [²] Exclusion of stone or infection | No = 0 | Absence of glandular swelling |
| | Low = 1 | Small glandular swelling with enlarged parotid (≤ 3 cm), or limited submandibular or lachrymal swelling |
| | Moderate = 2 | Major glandular swelling with enlarged parotid (> 3 cm), or important submandibular or lachrymal swelling |
| Articular [²] Exclusion of osteoarthritis | No = 0 | Absence of currently active articular involvement |
| | Low = 1 | Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min) |
| | Moderate = 2 | 1 to 5 (of 28 total count) synovitis |

| | | |
|--|--------------|---|
| | High = 3 | ≥ 6 (of 28 total count) synovitis |
| | No = 0 | Absence of currently active cutaneous involvement |
| Cutaneous [³] | | |
| Rate as “No activity” stable long-lasting features related to damage | Low = 1 | Erythema multiforma |
| | Moderate = 2 | Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus |
| | High = 3 | Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis |
| | No = 0 | Absence of currently active pulmonary involvement |
| Pulmonary [⁵] | | |
| Rate as “No activity” stable long-lasting features related to damage, or respiratory involvement not related to the disease (tobacco use etc.) | Low = 1 | Persistent cough or bronchial involvement with no radiographic abnormalities on radiography Or radiological or HRCT evidence of interstitial lung disease with: No breathlessness and normal lung function test. |
| | Moderate = 2 | Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NHYA II) or abnormal lung function tests restricted to: 70% >DL _{CO} ≥ 40% or 80% >FVC ≥ 60% |
| | High = 3 | Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NHYA III, IV) or with abnormal lung function tests: DL _{CO} < 40% or FVC < 60% |
| | No = 0 | Absence of currently active renal involvement with proteinuria < 0.5 g/d, no hematuria, no leucocyturia, no acidosis, or long-lasting stable proteinuria due to damage |
| Renal [⁵] | | |
| Rate as “No activity” stable long-lasting features related to damage, and renal involvement not related to the disease. | Low = 1 | Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/d) and without hematuria or renal failure (GFR ≥ 60 ml/min) |
| If biopsy has been performed, please rate activity based on histological features first | Moderate = 2 | Moderately active renal involvement, such as tubular acidosis with renal failure (GFR < 60 ml/min) or glomerular involvement with proteinuria between 1 and 1.5 g/d and without hematuria or renal failure (GFR ≥ 60 ml/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate |
| | High = 3 | Highly active renal involvement, such as glomerular involvement with proteinuria > 1.5 g/d or hematuria or renal failure (GFR < 60 ml/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinemia related renal involvement |
| | No = 0 | Absence of currently active muscular involvement |
| Muscular [⁶] | | |
| Exclusion of weakness due to corticosteroids | Low = 1 | Mild active myositis shown by abnormal EMG or biopsy with no weakness and creatine kinase (N < CK ≤ 2N) |
| | Moderate = 2 | Moderately active myositis proven by abnormal EMG or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N < CK ≤ 4N) |
| | High = 3 | Highly active myositis shown by abnormal EMG or biopsy with weakness (deficit ≤ 3/5) or elevated creatine kinase (> 4N) |
| | No = 0 | Absence of currently active PNS involvement |
| PNS [⁵] | | |
| Rate as “No activity” stable long-lasting features related to damage or PNS involvement not related to the disease | Low = 1 | Mild active peripheral nervous system involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia |
| | Moderate = 2 | Moderately active peripheral nervous system involvement shown by NCS, such as axonal sensory-motor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinemic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, inflammatory demyelinating polyneuropathy (CIDP) with mild functional impairment (maximal motor deficit of 4/5 or mild ataxia), Or cranial nerve involvement of peripheral origin (except trigeminal (V) neuralgia) |
| | High = 3 | Highly active PNS involvement shown by NCS, such as axonal sensory-motor neuropathy with motor deficit ≤ 3/5, peripheral nerve involvement due to vasculitis (mononeuritis multiplex etc.), severe ataxia due to ganglionopathy, inflammatory demyelinating polyneuropathy (CIDP) with severe functional impairment: motor deficit ≤ 3/5 or severe ataxia |
| | No = 0 | Absence of currently active CNS involvement |
| CNS [⁵] | | |
| Rate as “No activity” stable long-lasting features related to damage or CNS involvement not related to the disease | Low = 1 | Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis or multiple sclerosis-like syndrome with symptoms restricted to pure sensory impairment or proven cognitive impairment |
| | High = 3 | Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit. |
| | No = 0 | Absence of auto-immune cytopenia |
| Hematological [²] | | |
| For anemia, neutropenia, and thrombopenia, only auto-immune cytopenia must be considered | Low = 1 | Cytopenia of auto-immune origin with neutropenia (1000 < neutrophils < 1500/mm ³), and/or anemia (10 < hemoglobin < 12 g/dl), and/or thrombocytopenia (100,000 < platelets < 150,000/mm ³) |

| | |
|---|--|
| Exclusion of vitamin or iron deficiency, drug-induced cytopenia | Or lymphopenia ($500 < \text{lymphocytes} < 1000/\text{mm}^3$) |
| = 2 | Moderate Cytopenia of auto-immune origin with neutropenia ($500 \leq \text{neutrophils} \leq 1000/\text{mm}^3$), and/or anemia ($8 \leq \text{hemoglobin} \leq 10 \text{ g/dl}$), and/or thrombocytopenia ($50,000 \leq \text{platelets} \leq 100,000/\text{mm}^3$) Or lymphopenia ($\leq 500/\text{mm}^3$) |
| High = 3 | Cytopenia of auto-immune origin with neutropenia ($\text{neutrophils} < 500/\text{mm}^3$), and/or or anemia ($\text{hemoglobin} < 8 \text{ g/dl}$) and/or thrombocytopenia ($\text{platelets} < 50,000/\text{mm}^3$) |
| Biological [¹] | No = 0 Absence of any of the following biological feature |
| Low = 1 | Clonal component and/or hypocomplementemia (low C4 or C3 or CH50) and/or hypergammaglobulinemia or high IgG level between 16 and 20 g/L |
| = 2 | Moderate Presence of cryoglobulinemia and/or hypergammaglobulinemia or high IgG level $> 20 \text{ g/L}$, and/or recent onset hypogammaglobulinemia or recent decrease of IgG level ($< 5 \text{ g/L}$) |

CIDP= chronic inflammatory demyelinating polyneuropathy; CK= creatine kinase; CNS= central nervous system; DLCO= diffusing CO capacity; EMG= electromyogram; FVC= forced vital capacity; GFR= glomerular filtration rate; Hb= hemoglobin; HRCT= high-resolution computed tomography; IgG= immunoglobulin G; NCS= nerve conduction studies; NHYA= New York heart association classification; Plt= platelet; PNS=peripheral nervous system;