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Original article

Transcultural adaptation of the "EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI)" into Brazilian Portuguese

Érica Vieira Serrano[a,b,c], *Valéria Valim*[d,e,f,*], *Samira Tatiyama Miyamoto*[d,g], *Raquel Altoé Giovelli*[b,h], *Maurício Aquino Paganotti*[i], *Nágela Valadão Cadê*[j,k,l]

[a]*Post-graduation Program in Collective Health, Universidade Federal do Espírito Santo, Vitória, ES, Brazil*
[b]*Department of Internal Medicine, Escola Superior de Ciências, Santa Casa de Misericórdia de Vitória, Vitória, ES, Brazil*
[c]*Hospital Universitário Cassiano Antônio de Moraes, Vitória, ES, Brazil*
[d]*Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil*
[e]*Department of Internal Medicine, Universidade Federal do Espírito Santo, Vitória, ES, Brazil*
[f]*Rheumatology Outpatient Clinic, Hospital Universitário Cassiano Antônio de Moraes, Vitória, ES, Brazil*
[g]*Discipline of Physical Therapy, Universidade Federal do Espírito Santo, Vitória, ES, Brazil*
[h]*Master's Degree Program in Medicine, Universidade Federal do Espírito Santo, Vitória, ES, Brazil*
[i]*Post-graduation Program in Pharmaceutical Sciences, Universidade de Vila Velha, Vila Velha, ES, Brazil*
[j]*Post-graduation Program in Nursing, Universidade de São Paulo, São Paulo, SP, Brazil*
[k]*Discipline of Nursing, Universidade Federal do Espírito Santo, Vitória, ES, Brazil*
[l]*Post-graduation Program in Collective Health, Universidade Federal do Espírito Santo, Vitória, ES, Brazil*

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ABSTRACT

Introduction: The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) is an index of primary Sjögren's syndrome (PSS) systemic activity.
Objective: To perform the ESSDAI transcultural adaptation into Brazilian Portuguese.
Method: This was a cross-sectional study with 62 patients with PSS according to the criteria of the 2002 American-European Consensus. Six stages were conducted: conceptual, item, semantic, operational, functional, and measurement equivalences (interobserver reproducibility and construct validity). For the validity assessment, the ESSDAI was compared with the Physician's Global Assessment (PhGA), the Sjögren's Syndrome Disease Activity Index (SSDAI), and the Sjögren's Systemic Clinical Activity Index (SCAI). Patients were classified by a specialist physician into two groups according to disease activity (active and inactive), and according to the intention-to-treat (increase in therapy and no increase in therapy). The ESSDAI was tested in these groups. The following statistical tests were used: intraclass correlation coefficient (ICC), Bland-Altman plot for reproducibility, and Spearman's correlation coefficient (r_s) and Mann-Whitney's test for validity ($P < 0.05$ and 95% CI).
Results: The mean ESSDAI score was 4.95 ± 6.73. The reproducibility obtained a strong ICC of 0.89 and good agreement. When compared with other indices, it showed a strong r_s with PhGA (0.83; $P < 0.000$), a moderate r_s with SSDAI (0.658; $P < 0.000$) and a weak r_s with the SCAI (0.411; $P = 0.001$). The group "active" and the group " increase in therapy" had higher ESSDAI values ($P = 0.000$).

* *Corresponding author.*
E-mail: val.valim@gmail.com (V. Valim).

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Conclusion: The Brazilian Portuguese version of ESSDAI was shown to be adaptable, reproducible, and valid for this language.

Adaptação transcultural do "EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI)" para a língua portuguesa

Palavras-chave:
Síndrome de Sjögren
Escalas
Estudos de validação
ESSDAI

RESUMO

Introdução: O EULAR *Sjögren's Syndrome Disease Activity Index* (ESSDAI) é um índice de atividade sistêmica da síndrome de Sjögren primária (SSP).
Objetivo: Realizar a adaptação transcultural do ESSDAI para a língua portuguesa.
Método: Estudo transversal com 62 pacientes com SSP de acordo com consenso europeu-americano de 2002. Foram realizadas seis etapas: equivalência conceitual, de item, semântica, operacional, funcional e de mensuração (reprodutibilidade interobservador e a validade de constructo). Para a validade, o ESSDAI foi comparado com a avaliação global do médico (PhGA), o Sjögren's Syndrome Disease Activity Index (SSDAI) e o *Sjögren's Systemic Clinical Activity Index* (SCAI). Os pacientes foram classificados por um médico especialista conforme a atividade da doença em dois grupos, "ativo" e "inativo", e conforme a intenção de tratar nos grupos "aumento de terapia" e "sem aumento de terapia". O ESSDAI foi testado nesses grupos. Utilizou-se os testes estatísticos: coeficiente de correlação intraclasse (CCI) e método de Bland Altman para a reprodutibilidade; e coeficiente de Spearman (r_s) e teste de Mann-Whitney para a validade (P < 0,05 e IC 95%).
Resultados: A média do ESSDAI foi de 4,95 ± 6,73. A reprodutibilidade obteve um forte CCI de 0,89 e boa concordância. Na comparação com outros índices, apresentou forte coeficiente de Spearman com o PhGA (r_s = 0,83; P < 0,000), moderado com o SSDAI (r_s = 0,658 ; P < 0,000) e fraco com o SCAI (r_s = 0,411; P = 0,001). O grupo "ativo" e o grupo "com aumento de terapia" obtiveram maiores valores de ESSDAI (P = 0,000).
Conclusão: a versão em português do ESSDAI mostrou ser adaptável, reprodutível e válida para a língua portuguesa.

Introduction

Primary Sjögren's syndrome (PSS) is the second most common autoimmune rheumatic disease,[1] after rheumatoid arthritis, with an estimated prevalence in the Brazilian population of 0.17%.[2] However, due to the scarcity of studies focused on the treatment of its systemic manifestations, PSS still has treatment directed to its dryness manifestations. This limitation arises from the lack of appropriate tools to assess the systemic activity of PSS. [3,4] Moreover, the few studies published on PSS used different methods to measure the same parameter, creating a heterogeneous field of results within the same subject, which prevents the progress of research in the construction of knowledge.[5] Therefore, validated tools assessing PSS activity are necessary[6,7] to evaluate the effectiveness of new therapies that focus both on severe systemic [8-12] and glandular [8,13,14] manifestations.

The European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) was constructed from a study consensus of the EULAR group and North-American for the study of PSS, and aims to quantify systemic disease activity. It comprises 12 areas: constitutional, lymphadenopathy, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral nervous system, central nervous system, hematological, and biological. These areas are scored based on clinical parameters evaluated by the physician.[15]

The transcultural adaptation of tools developed in another culture or language is not restricted to a simple translation of the original item. The process should contain a sequence of the following equivalence steps:[16] conceptual and item equivalence (whether domains, concepts, and items assess the same parameters in both languages); semantic equivalence (whether words or phrases have the same meaning; comprising the following steps: translation, back-translation, discussion with experts, and pre-test); operational equivalence (whether the format, instructions, administration and measurement methods are equivalent in both cultures); measurement (testing the psychometric properties); and functional equivalence (whether the original tool and summarized version are equivalent).

In measurement equivalence, the psychometric properties assessed are reproducibility (whether measures of individuals at different times and in different circumstances produce the same or similar results) and validity (whether the test is actually measuring what it intends to measure).[5,17]

In preliminary studies of tool construction, ESSDAI was proven to be a tool with high content validity, good construct validity and reproducibility, with a clear and objective scor-

ing system, good association of their domains with disease activity, and better responsiveness and accuracy to detect changes in the activity of the patients compared to previous tools.[11,15,18-22]

In addition to the need for validation of this tool, it is essential that its properties are tested in several languages and in different populations of patients with PSS. This allows for the performance of transcultural studies and comparisons between national and international studies, thus providing scientific communication between countries of different languages.[23] Currently, the ESSDAI has been published only in the English language; this study aimed to perform its transcultural adaptation into Brazilian Portuguese.

Method

This was a cross-sectional observational study approved by the Research Ethics Committee of the Centro de Ciências da Saúde of the Universidade Federal do Espírito Santo (UFES), in 2010, and developed at the Sjögren's syndrome outpatient clinic of the Rheumatology Service of the Hospital Universitário Cassiano Antonio de Moraes, in Vitória, state of Espírito Santo, Brazil.

The procedures to perform the transcultural adaptation of ESSDAI followed the methodology proposed by Herdman et al.,[16] which covers six steps: conceptual, item, semantic, operational, measurement, and functional equivalences.

Twenty patients were selected for the semantic equivalence, and 62 patients for the evaluation of measurement equivalence. Inclusion criteria were: diagnosis of PSS based on the European-American classification criteria for Sjögren's syndrome,[24] age equal to or greater than 18 years, and signing of the informed consent. Patients with other concomitant autoimmune diseases were excluded.

The sample was calculated based on the use of at least five patients per domain of the tool,[25] in a total of 62 patients, with 57 patients from the Sjögren's syndrome outpatient clinic of the Rheumatology Service of HUCAM, two from other teaching hospitals, and three from private practices. Among the 115 patients enrolled in the service, 30 did not meet the inclusion criteria and 28 were not found to participate in the interview.

The conceptual, item, semantic, and operational equivalences of ESSDAI were verified at the time of the translation and back-translation by a committee comprising a rheumatologist, a physical therapist specialized in Rheumatology, both of whom had experience managing patients with PSS and were fluent in English, and an English teacher. The translation of the ESSDAI was performed independently by two English teachers whose native language is Brazilian Portuguese, and who were aware of the purpose of the study. At the back-translation, this version was submitted to translation into English by two other English teachers, whose native language is English, blinded to the original version and to the study objective.

In the pretest, the consensus version in Portuguese was applied to 20 consecutive patients diagnosed with PSS by a rheumatologist experienced in the management of these patients.

In the measurement equivalence, the psychometric properties were compared to the original tool, according to Streiner and Norman[5] and Kirshner and Guyatt[17]. The evaluated properties were reliability (interobserver reproducibility) and construct validity. The 62 patients underwent medical consultation, and the Physician Global Assessment (PhGA), ESSDAI, Sjögren's Systemic Clinical Activity Index (SCAI),[18] and Sjögren's Syndrome Disease Activity Index (SSDAI)[19] tools were completed on the same day by two independent rheumatologists (examiner A and B) experienced in the management of patients with PSS who were blinded and in separate rooms. The tools were scored from 0 to 10 for PhGA, 0 to 123 for ESSDAI, 0 to 72 for SCAI, and 0 to 21 for SSDAI.[15,18,19]

For construct validity, the ESSDAI was compared with the following tools: numerical PhGA, and SSDAI and SCAI translated into Brazilian Portuguese.[26,27] Subsequently, the sample was divided into two groups (active and inactive) according to the onset or worsening of potentially reversible signs and symptoms of the disease in the past four weeks, as defined by a medical specialist.

The ESSDAI was also compared with the "intention to treat" on the day of medical assessment compared to the previous evaluation. Intention to treat was defined as a change in therapy, whether change in drug dosage, drug withdrawal, or inclusion of a new drug. The medications of interest were immunosuppressants, hydroxychloroquine, oral or intravenous corticosteroids, immunoglobulins, and biological agents. The sample was classified into two groups: increase and non-increase of therapy.

The collected data were analyzed and processed with the Statistical Package for Social Sciences (SPSS), release 19.0. The intraclass correlation coefficient (ICC), Bland-Altman plots, and weighted kappa were used for interobserver reproducibility. Spearman's coefficient was used for construct validity, when comparing ESSDAI with numerical PhGA, SCAI, and SSDAI.[28] Mann-Whitney's test was used to test ESSDAI in the comparison between the "active" and "inactive" groups and between the "increase in therapy" and "non-increase in therapy" groups.[28] A P-value ≤ 0.05 was considered to be statistically significant in all analyses.

Results

There were no differences between the versions in the two languages regarding the phases of item, conceptual, semantic, and operational equivalences; and thus the final consensual Brazilian version was obtained.

Demographic characteristics and disease manifestations of the 62 patients are shown in Table 1.

Regarding the study's interobserver reproducibility, a strong and significant intraclass correlation coefficient (0.898) was obtained between the two examiners when assessing the total ESSDAI score, showing high reproducibility. The analysis by the Bland-Altman plot (Fig. 1) presented a good interobserver agreement of ESSDAI, with only three patients outside the standard deviation interval of ± 1.96 (outliers).

Weighted kappa was used for the interobserver correlation regarding the different domains of ESSDAI. There was no agreement in the lymphadenopathy domain; in the constitutional domain, the agreement was low (kappa: 0.1-0.4); in the glandular and articular domains, it was moderate (kappa:

0.41-0.60); and in the cutaneous, respiratory, renal, peripheral nervous system, hematological, and biological domains there was good agreement (kappa: 0.61 to 0.8) (Table 2). The renal and cutaneous domains showed the highest agreement, 0.791 and 0.792, respectively.

Table 1 – Characteristics and disease manifestations of 62 patients with PSS.

Characteristics	n (%) or mean ± SD
Age (years)	49.4 ± 11.6
Female gender	62 (100)
Disease duration	7.2 ± 5.4
Objective ocular dryness	48 (77.4)
Objective oral dryness	53 (85.5)
Lymphocytic sialadenitis ≥ one focus-score	56 (90.3)
Anti-Ro antibody	27 (43.6)
Anti-La antibody	12 (19.4)
Positive antinuclear factor	48 (77.4)
Rheumatoid factor	14 (21.6)
Active disease by specialist	33 (53.2)
Numerical PhGA	1.82 ± 1.87
ESSDAI	4.95 ± 6.73
SSDAI	1.71 ± 1.89
SCAI	4.85 ± 3.00
Frequency of systemic manifestations	
Constitutional	6 (9.7)
Lymphadenopathy	1 (1.6)
Glandular	5 (8.1)
Articular	17 (27.4)
Cutaneous	3 (4.8)
Respiratory	9 (14.5)
Renal	5 (8.1)
Muscular	0
Peripheral nervous system	7 (11.3)
Central nervous system	0
Hematological	25 (40.3)
Biological	25 (40.3)
Fatigue	48 (77)

PSS, primary Sjögren's syndrome; SD, standard deviation; PhGA, Physician Global Assessment; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; SCAI, Sjögren's Systemic Clinical Activity Index; SSDAI, Sjögren's Syndrome Disease Activity Index.

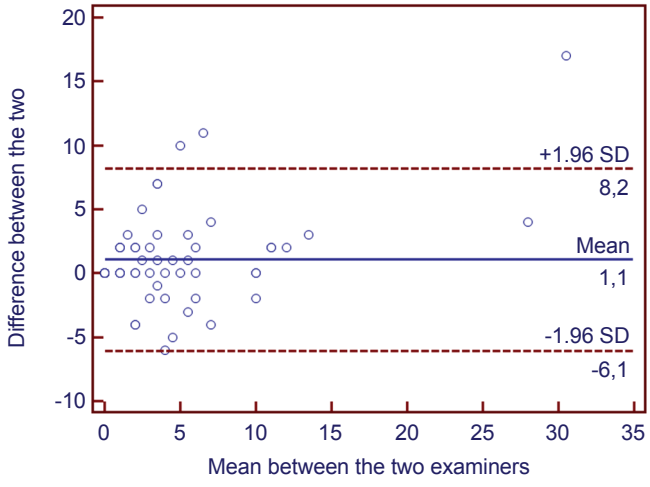

Fig. 1 – Agreement between ESSDAI score measurements between two examiners using the Bland-Altman method.

For construct validity, in comparison with numerical PhGA, a strong Spearman's coefficient of 0.832 (P < 0.000) was obtained; a moderate result was obtained with SSDAI (0.658, P < 0.000), and a weak result with SCAI (0.411, P = 0.001) - Table 3.

Table 4 presents the mean and median of ESSDAI; in the active group, it was greater than in the inactive group by nominal PhGA, and there was a statistically significant difference between the groups (P = 0.000). The active group had the highest mean rank in the ESSDAI when compared to the inactive group.

When comparing the ESSDAI according to the intention to treat between the groups, a statistically significant difference was observed between the groups (P = 0.000) (Table 4). The group with increase in therapy had higher ESSDAI values when compared to the group with no increase in therapy.

Discussion

There were no differences in the interpretation and , since it is a tool with mostly clinical domains, which are technical and objective in nature, with clear language and good understanding by the physician.

The demographic and clinical characteristics of the 62 patients were similar to those found in other studies of PSS tools (SCAI, SSDAI) and cohorts of patients with a prevalence of women > 93%; mean age 47 to 59 years; long disease duration, with a mean of 7.2 years;[15,18,19,22,29-33] and mean interval between symptom onset and diagnosis of five years, which demonstrates a long delay in the diagnosis of this disease, previously reported by other authors.[34]

There was a high prevalence of dryness, confirmed by objective testing and high positivity of minor salivary gland biopsy (90.3%), similar to other studies.[15,18]

One of the difficulties of validation studies of PSS activity tools, such as the SCAI and SSDAI, is that most of the study patients had inactive or slightly active disease.[15,18,19,29] The total ESSDAI score ranges from 0 to 123. In the Argentinean study of ESSDAI validation into Spanish, a mean ESSDAI score of 5 was observed (ranging from 3 to 9), as well as a mean PhGA of 1.0 (0.4 to 2.2), that is, a prevalence of patients with low disease activity and inactivity.[29] Cohorts from different

Table 2 – Results of interobserver agreement per ESSDAI domain.

Domains	Weighted kappa
Constitutional	0.212[a]
Lymphadenopathy	-0.016
Glandular	0.588[a]
Articular	0.450[a]
Cutaneous	0.792[a]
Respiratory	0.638[a]
Renal	0.791[a]
Muscular	-
Peripheral nervous system	0.759[a]
Central nervous system	-
Hematological	0.693[a]
Biological	0.693[a]

[a]Statistically significant kappa, P < 0.05.

Table 3 – Descriptive measures and correlation of ESSDAI with other tools in PSS.

Variables	Mean (±)	Minimum	Median	Maximum	Spearman's coefficient	P-value
ESSDAI	4.95 ± 6.73	0	3	39	---	---
Numerical PhGA	1.82 ± 1.87	0	1	7	0.832	(P < 0.000)
SSDAI	1.71 ± 1.89	0	1	8	0.658	(P < 0.000)
SCAI	4.85 ± 3.00	1	4.5	16	0.411	(P = 0.001)

Scores of tools: PhGA: 0-10 (Pincus et al., 2008); ESSDAI: 0-123 (Seror et al., 2010b); SSDAI: 0-21 (Vitali et al., 2007); SCAI: 0-72 (Bowman et al., 2007). PSS, primary Sjögren's syndrome; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; PhGA, Physician Global Assessment; SSDAI, Sjögren's Syndrome Disease Activity Index; SCAI, Sjögren's Systemic Clinical Activity Index.

Table 4 – Descriptive measures and Mann-Whitney's test for ESSDAI in groups according to activity by nominal PhGA and intention to treat.

	ESSDAI - Total score							
	n	Minimum value	Maximum value	Median	Mean	SD	Mid posts	P-value[a]
Nominal PhGA								
Inactive	29	0	7	0.00	1.21	1.68	17.14	0.000
Active	33	1	39	6.00	8.24	7.75	44.12	
Intention to treat								
Increase in therapy	11	5	39	10.00	13.18	11.12	52.05	0.000
No increase in therapy	51	0	15	2.00	3.18	3.53	27.07	

ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; PhGA, Physician Global Assessment; SD, standard deviation.
[a]Mann-Whitney test.

countries where ESSDAI was applied showed a mean of: 4 (0 to 43) in the English, 5.7 (0 to 29) in the French, 3.18 (0 to 29) in the Dutch, and 11.1 (0 to 37) in the Finnish cohort; [30,31,33,35] all these samples showed patients with low disease activity.

In the ESSDAI construction study, the mean total score was 15.5 (2 to 47), with only 25% of patients with a score ≥ 13.[15] In the present study, 46.8% of the patients included had systemic manifestations at the moment of inclusion, and 61.3% had already had a disease flare. At the time of evaluation, active disease was detected in 53.2% according to the nominal PhGA; however, there was a predominance of low activity, which was observed in 38.7% of patients. This low activity was confirmed by the mean numerical PhGA score of 1.92 and the mean total ESSDAI score of 4.95 (0 to 39), with 11.3% of patients with a score ≥ 12, similar results to those of the Argentinean validation study.[29]

Disease activity in PSS is more difficult to detect than in other systemic rheumatic diseases, such as systemic lupus and rheumatoid arthritis, and the clinical course of PSS is usually more insidious.[36] Furthermore, it can be observed that systemic manifestations are observed in only one-third of patients with PSS, which can hinder the inclusion of a large number of patients in the studies. One way to solve this problem would be to perform multicenter national or international studies, to attain a better composition of the research sample.

The study interobserver reproducibility was substantial between the two examiners (ICC = 0.898). In the Argentinean validation study, reproducibility was good, but lower, with an ICC = 0.67 (P = 0.06) for ESSDAI.[29] Regarding other PSS activity tools, the SSDAI validation study did not assess reproducibility, and the SCAI study obtained a good correlation of 0.71.[18,19] Although these results did not present a strong correlation (ICC > 0.8), they are still better than the reproducibility results of PhGA in PSS in the literature, which showed an ICC = 0.41.[15] The disease assessment by the physician through PhGA is subject to considerable variability, as it is greatly influenced by the patient's symptoms such as fatigue and pain, which are subjective parameters that are difficult to measure and highly variable in such a polymorphic disease. This also justifies the need for the validation of a more objective tool that includes systemic manifestations, such as ESSDAI, to be used in different situations, by different physicians, whether experienced or not.

When analyzing the results of ESSDAI interobserver agreement by the Bland-Altman method, a good agreement was obtained; however, the mean difference between examiners was 1.1. This indicates that there may have been a score overestimation by one examiner in relation to the other. Some hypotheses to explain this result are the difference in time of experience in the clinical management of PSS between the examiners and the absence of tool calibration between the two examiners.

There are no similar studies in the literature to compare whether an error variation of 1.1 between examiners for ESSDAI is clinically relevant or not. Furthermore, this tool does not have stratification values of its total score or an established cutoff to define disease activity. After the cutoff value and the clinically important minimal difference are established by an international multicenter ESSDAI validation study that will soon be completed, the difference between examiners can be better interpreted regarding clinical relevance.

The interobserver reproducibility per ESSDAI domain demonstrates that the agreement was satisfactory in the six domains, i.e., they had a large number of cases whose result was the same among examiners (weighted kappa between 0.61 and 0.8). No other studies were found in the literature that performed this domain-by-domain comparison for PSS tools.

The two domains with regular agreement, the glandular and articular domains, contain subjective parameters that

may have influenced the outcome. In the glandular domain, the distinction between mild or significant increase in glandular, submandibular, and lacrimal volume is at the examiner's discretion, which can generate an over- or underestimation from one examiner in relation to the other. In the articular domain, the item "arthralgia in hands, wrists, ankles, and feet accompanied by morning stiffness > 30 minutes" is a parameter answered by the patient, which can be a source of bias between examiners, as the patient may have other causes of associated joint pain, causing an examiner to score differently from the other.

The sample showed a frequency of associated fibromyalgia of 43.5% (n = 27) and patients with comorbidities were not excluded. Nevertheless, it is worth remembering that the tool itself asks not to take into account other causes of joint pain, such as osteoarthritis and fibromyalgia,[15] frequently found in individuals with PSS.

Another factor that may have contributed to little or no agreement in some domains was the lack of training of the two examiners on individual items prior to the application or calibration. In some similar studies, the physicians were trained to score the tools to improve their reproducibility;[18,37,38] however, in order to simulate and adhere to daily clinical practice, the authors chose not to perform the calibration in this study.

The ESSDAI tool is a formative model, in which the items themselves have no value, but rather are assembled together to constitute a final construct.[39] This construct, measured by the total score, should have adequate reliability and reproducibility. When these items are evaluated individually, there may not be complete agreement, as examiners may disagree on an item and agree on others. What should be ultimately considered, thus, is the agreement of the tool's total score.[5]

The construct validity of ESSDAI with PhGA was good (coefficient 0.83, $P < 0.000$), and slightly better than that found in the ESSDAI construction study (0.61, $P < 0.001$)[15] and in the Argentinean validation study (0.79, $P < 0.01$).[29] The validity of SSDAI with PhGA showed similar results (0.87, $P < 0.0001$).[19] The construct validity of ESSDAI with SSDAI was moderate, whereas it was weak with SCAI. This result can be explained in part by the limitations of the method, as the SCAI and SSDAI are not the gold standard for comparing validity data. They are transition tools that did not achieve good results in their psychometric properties, as they showed low content validity and reproducibility. Moreover, the SCAI has patient-reported subjective items such as fatigue, morning stiffness, dyspnea, and Raynaud's phenomenon, which may have contributed to its poor correlation with ESSDAI.

Any measure of validity that is performed will show some associated error, and as a consequence, it should be expected that the correlation between tools of the same attribute should achieve a mean between 0.4 and 0.8. Any correlation lower than that suggests that the reliability of one or the other tool is unacceptably low, or that they are measuring different phenomena.[5,24] Thus, the coefficient of 0.411 found for SCAI is within the minimally acceptable limit suggested by the literature.

When evaluating validity between groups, ESSDAI was able to discriminate between active and inactive groups classified by PhGA, and by intention to treat and therapeutic change by the expert physician, despite the low variability of patients and the sample size. A mean of 1.2 was obtained in the inactive group and of 8.2 in the active group, with significant difference ($P < 0.05$), i.e., higher values of ESSDAI accompany higher values of disease activity assessed by the physician, as well as greater use of immunosuppressive therapy. There are no other studies in the literature that used this type of evaluation per groups for ESSDAI to compare these results.

Currently, ESSDAI has been applied to several European cohorts,[30,31,40,41] and the tendency of recommendations is to use it in practice and medical research, not alone, but together with other activity parameters such as the EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI) symptom questionnaire,[42] objective tests of saliva (sialometry sialochemistry) and tears (ocular dryness score), and laboratory parameters of autoimmune inflammation (measurement of cytokines, gammaglobulins, IgG, and β2 microglobulins).[11,43] Its multicenter validation, which is in progress, as well as its translation into different languages, are crucial to achieve a uniform scientific language in different countries and to compare studies, in order to facilitate clinical research on PSS.

Conclusion

This study demonstrated that the use of ESSDAI in the evaluated sample, which had demographic and clinical characteristics similar to other populations from PSS activity index studies, showed a strong correlation with the overall assessment of activity scored by the physician and was able to discriminate active from inactive patients in the Brazilian setting.

The authors conclude that the Brazilian Portuguese version of ESSDAI was shown to be adaptable, reproducible, and valid for this language.

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Conflicts of interest

The authors declare no conflicts of interest.

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Appendix – EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI).

Constitutional domain (3)
Please, be careful not to evaluate constitutional symptoms unrelated to the disease (such as fever of infectious origin, voluntary weight loss).

No activity	Absence of the following symptoms:	☐ 0
Low activity	Mild or intermittent fever (37.5°-38.5°C) / night sweats and/or involuntary weight loss of 5% to 10% of body weight	☐ 1
Moderate activity	Severe fever (> 38.5°C) / night sweats and/or involuntary weight loss of > 10% of body weight	☐ 2

Lymphadenopathy domain (4)

No activity	Absence of the following features:	☐ 0
Low activity	Lymphadenopathy ≥ 1 cm in any nodal region or ≥ 2 cm in inguinal region	☐ 1
Moderate activity	Lymphadenopathy ≥ 2 cm in any region or ≥ 3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging)	☐ 2
High activity	Current malignant B-cell proliferative disorder	☐ 3

Glandular domain (2)
Please be careful not to evaluate increased glandular volume unrelated to the disease (such as lithiasis or infection).

No activity	Absence of glandular swelling	☐ 0
Low activity	Small glandular swelling with: • enlarged parotid (≤ 3 cm), or discrete submandibular or lachrymal swelling[a]	☐ 1
Moderate activity	Major glandular swelling with: • enlarged parotid (> 3 cm), or important submandibular or lachrymal swelling[a]	☐ 2

Articular domain (2)
Please be careful not to evaluate joint involvement unrelated to the disease, such as osteoarthritis.

No activity	Absence of currently active articular involvement	☐ 0
Low activity	Arthralgia in hands, wrists, ankles and feet accompanied by morning stiffness (> 30 min)	☐ 1
Moderate activity	1 to 5 (of 28 total count) synovitis[b]	☐ 2
High activity	≥ 6 (of 28 total count) synovitis[b]	☐ 3

Cutaneous domain (3)
Please be careful not to evaluate as "No activity" old and stable lesions that are more related to the damage (sequelae) than to the disease activity or cutaneous involvement unrelated to the disease.

No activity	Absence of currently active cutaneous involvement	☐ 0
Low activity	Erythema multiforme	☐ 1
Moderate activity	Limited cutaneous vasculitis, including urticarial vasculitis[c], purpura limited to feet and ankle, or subacute cutaneous lupus	☐ 2
High activity	Diffuse cutaneous vasculitis, including urticarial vasculitis[c], diffuse purpura, or ulcers related to vasculitis	☐ 3

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Appendix – EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) *(continued)*.

Respiratory domain (5) Please be careful not to evaluate as "No activity" stable and old lesions more related to the damage (sequelae) than with disease activity or respiratory involvement unrelated to disease (ex. cigarette smoking).		
No activity	Absence of currently active pulmonary involvement	☐ 0
Low activity	Persistent cough or bronchial involvement with no radiographic abnormalities on common X-ray or evidence of interstitial lung disease at plain x-ray or high resolution computed tomography (HRCT) with: • No breathlessness, and • normal lung function test.	☐ 1
Moderate activity	Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with • shortness of breath on exertion (NHYA[d] II) or abnormal lung function tests restricted to: 70% > DLCO[e] ≥ 40% or 80% > FVC[f] ≥ 60%	☐ 2
High activity	Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with: • shortness of breath on small exertion or rest (NHYAd III, IV) or abnormal lung function tests: DLCO[e]< 40% or FVC[f]< 60%	☐ 3
Renal domain (5) Please be careful not to evaluate as "No activity" stable and old lesions that are more related to the damage (sequelae) than with disease activity and renal involvement unrelated to the disease. If a biopsy is performed, please classify the activity based primarily on histological characteristics.		
No activity	Absence of currently active renal involvement with: • proteinuria < 0.5 g/d, no hematuria, no leukocyturia, no acidosis, or • long-lasting stable proteinuria due to damage/sequelae	☐ 0
Low activity	Evidence of specific renal activity involvement, limited to: • tubular acidosis without renal failure, or • glomerular involvement - with proteinuria (between 0.5 and 1 g/dL), and - without hematuria or renal failure (GFR[g] ≥ 60 mL/min)	☐ 1
Moderate activity	Moderate renal activity: • tubular acidosis with renal failure (GFR[g] < 60 mL/min), or • glomerular involvement: - with proteinuria between 1 and 1.5 g/d, and - no hematuria or renal failure (GFR[g] ≥ 60 mL/min) • histological evidence: - glomerulonephritis, and/or - important interstitial lymphoid infiltrate	☐ 2
High activity	High renal activity: • glomerular involvement: - proteinuria > 1.5 g/dL, and/or - hematuria, and/or - renal failure (GFR[g]< 60 mL/min), or • histological evidence of: - proliferative glomerulonephritis, or - cryoglobulinemia related to renal involvement	☐ 3
Muscular domain (6) Please be careful not to evaluate muscle involvement unrelated to the disease, such as weakness due to corticosteroids.		
No activity	Absence of currently active muscle involvement	☐ 0
Low activity	Mild active myositis shown by abnormal EMG or biopsy with: • no weakness and altered creatine kinase (N < CK ≤ 2N)	☐ 1
Moderate activity	Moderately active myositis proven by abnormal EMG or biopsy with: • weakness (maximal deficit of 4/5), or elevated creatine kinase (2N < CK ≤ 4N),	☐ 2
High activity	Highly active myositis shown by abnormal EMG or biopsy with: • weakness (deficit ≤ 3/5) or elevated creatine kinase (> 4N)	☐ 3

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Appendix – EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) *(continued)*.

Peripheral nervous system (PNS) domain (5) Please be careful not to evaluate as "No activity" stable and old lesions that are more related to the damage (sequelae) than to the activity or involvement of the peripheral nervous system unrelated to the disease.		
No activity	Absence of currently active PNS involvement	☐ 0
Low activity	Evidence of mild active peripheral nervous system involvement, such as: • axonal peripheral polyneuropathy diagnosed by NCS/EMG, or • trigeminal (V) neuralgia	☐ 1
Moderate activity	Evidence of moderately active involvement of the peripheral nervous system, such as: • motor and sensory axonal neuropathy diagnosed by NCS / EMG, without motor deficit, or • pure sensory neuropathy with presence of cryoglobulinemic vasculitis or • ganglionopathyh with symptoms restricted to moderate ataxia, or • chronic inflammatory demyelinating polyneuropathy (CIDP)[i] with moderate functional disability (without motor deficit or moderate ataxia), or • peripheral cranial nerve involvement - except trigeminal nerve (V)	☐ 2
High activity	Evidence of highly active involvement of the peripheral nervous system, such as: • motor and sensory axonal neuropathy diagnosed by NCS/EMG with motor deficit ≤ 3/5, or • peripheral nerve involvement attributed to vasculitis (mononeuritis multiplex), or • severe ataxia attributed to ganglionopathy[h] or • CIDP[i] with severe functional disability: motor deficit ≤ 3/5 or severe ataxia	☐ 3
Central nervous system (CNS) domain (5) Please be careful not to evaluate as "No activity" stable and old lesions that are more related to the damage (sequelae) than to the disease activity or involvement of the central nervous system unrelated to the disease.		
No activity	Absence of currently active CNS involvement	☐ 0
Moderate activity	Moderately active CNS manifestations, such as: • involvement of cranial nerve or central origin, or • optical neuritis, or • multiple sclerosis-like syndrome with symptoms restricted to pure sensory impairment or proven cognitive impairment	☐ 1
High activity	Highly active CNS manifestations, such as: • cerebral vasculitis with cerebrovascular accident or transient ischemic attack • seizures, or • transverse myelitis, or • lymphocytic meningitis, or • multiple sclerosis-like syndrome with motor deficit.	☐ 2
Hematological domain (2) Please note: taking into account anemia, neutropenia and thrombocytopenia, only autoimmune cytopenia should be considered; do not evaluate cytopenia that is unrelated to the disease (such as vitamin or iron deficiency, and drug-induced cytopenia, e.g., lymphocytopenia associated with cyclophosphamide).		
No activity	Absence of auto-immune cytopenia	☐ 0
Low activity	Cytopenia of auto-immune origin with: • neutropenia[j] (1,000 < neutrophils < 1,500/mm³), and/or anemia[k] (10 < Hb < 12 g/dL), or thrombocytopenia[l] (100,000 < platelets < 150,000/mm³), or lymphopenia (500 < lymphocytes < 1,000/mm³)	☐ 1
Moderate activity	Cytopenia of auto-immune origin with: • neutropenia[j] (500 ≤ neutrophils ≤ 1,000/mm³), or anemia[k] (8 ≤ Hb ≤ 10 g/dL), or thrombocytopenia[l] (50,000 ≤ platelets ≤ 100,000/mm³), or lymphopenia (≤ 500/mm³)	☐ 2
High activity	Cytopenia of auto-immune origin with: • neutropenia[j] (neutrophils < 500/mm³), or anemia[k] (Hb < 8 g/dL) or thrombocytopenia[l] (platelets < 50,000/mm³)	☐ 3

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Appendix – EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) *(continued)*.

Biological domain (1)

No activity	Absence of any of the following biological alterations:	☐ 0
Low activity	• Clonal component and/or hypocomplementemia (low C4 or C3 or CH50) or hypergammaglobulinemia or high IgG level between 1,600 and 2,000 mg/dL	☐ 1
Moderate activity	• Presence of cryoglobulinemia and/or hypergammaglobulinemia or high IgG level > 2,000 mg/dL, or recent[m] onset of hypogammaglobulinemia or recent decrease of IgG level (< 500 mg/dL)	☐ 2

N, normal (reference value); EMG, electromyography.

[a]The distinction between discrete or major swelling of submandibular or lacrimal gland volume is at the physician's discretion.

[b]The 28 articulations included in the calculation of the Disease Activity Score 28are shoulders, elbows, wrists, metacarpophalangeal, proximal interphalangeal and knee joints.

[c]Limited cutaneous vasculitis involves < 18% of body surface area (BSA), diffuse cutaneous vasculitis involves > 18% of BSA. BSA is defined using the rule of nines (used to assess the extent of burns) as shown below: palm (excluding fingers) = 1% BSA; each lower limb = 18%; each upper limb = 9%; trunk (frontal) = 18% BSA; trunk (dorsal) = 18% BSA.

For the diagnosis of interstitial lung disease, High Resolution Computed Tomography or plain radiography are necessary and must have been performed within the last two years.

[d]NYHA (New York Heart Association functional classification).

[e]DLCO (Lung Diffusion Capacity Testing).

[f]FVC (Forced Vital Capacity).

[g]Glomerular filtration rate (GFR) calculated through the Modification of Diet in Renal Disease (MDRD) formula.

[h]Pure sensory disability with ataxia and diffuse disability or abolition of sensory potential in nerve conduction study (NCS)

[i]Polyradiculoneuropathy with suggestive clinical symptoms (sensorimotor deficit in the four limbs, proximal motor deficit, generalized areflexia, early sensory symptoms affecting the upper limbs, and/or associated with cranial nerve involvement), increased protein level and/or abnormal NCS (prolonged motor distal latency, reduced nerve conduction velocity, prolonged F wave latency, conduction blockade and/or temporal dispersion).

[j]Neutropenia of unknown etiology.

[k]Anemia with positive Coombs' test and increased reticulocyte count

[l]Thrombocytopenia of peripheral origin with no other known etiology, or in case of difficult to perform identification of anti-platelet autoantibodies and/or presence of megakaryocytes in bone marrow aspirate and/or associated autoimmune anemia.

[m]In the last six months.