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Running head: Determinants of HR-QoL in active pSS

**Severe Health-Related Quality-of-life Impairment in Active Primary Sjögren's
Syndrome Is Driven by Patient-Reported Outcomes: Data from a Large Therapeutic
Trial**

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Abstract (249 words)

Objectives: To identify the principal determinants of health-related quality-of-life [HR-QoL] impairment in patients with active primary Sjögren's syndrome [pSS] participating in a large therapeutic trial [TEARS].

Methods: At the inclusion visit for the TEARS trial, 120 patients with active pSS completed the Short Form survey 36 [SF36], a validated HR-QoL assessment tool. Univariate then multivariate linear regression analyses were used to assess associations linking SF36 physical and mental components to demographic data, patient-reported outcomes [symptom intensity assessments for dryness, pain and fatigue, including the EULAR SS Patient Reported Index (ESSPRI)], objective measures of dryness and autoimmunity, and physician evaluation of systemic activity [using the EULAR SS Disease Activity Index (ESSDAI)].

Results: SF36 scores indicated marked HR-QoL impairments in our population with active pSS. Approximately 1/3 of the patients had low, moderate and high systemic activity according to the ESSDAI. ESSPRI and ESSDAI scores were moderately but significantly correlated. The factors most strongly associated with HR-QoL impairment were patient-reported symptoms, best assessed using the ESSPRI, with pain and ocular dryness intensity showing independent associations with HR-QoL. Conversely, systemic activity level was not associated with HR-QoL impairment in multivariate analyses, even in the patient subset with ESSDAI values indicating moderate-to-high systemic activity.

Conclusions: The cardinal symptoms of pSS (dryness, pain and fatigue, best assessed using the ESSPRI) are stronger predictors of HR-QoL impairment than systemic involvement (assessed by the ESSDAI), and should be used as endpoints in future therapeutic trials focusing on patients' well-being. New consensual and data-driven response criteria are needed for pSS studies.

Significance and Innovations.

- Patients with active pSS experience severe quality of life impairment.
- Patients with high systemic activity (as evaluated by the physician using the ESSDAI score) also report more intense symptoms (mostly pain and fatigue, assessed using the ESSPRI score).
- The intensity of symptoms (as assessed with ESSPRI) is a stronger determinant of HR-QoL impairment than systemic involvement assessed with ESSDAI. Primary endpoints for future therapeutic trials should use the ESSPRI if focusing on patients' well-being, and the ESSDAI or one of its subscales for patients with forefront systemic involvement.
- New consensual and data-driven response criteria, which could combine the validated ESSPRI and ESSDAI activity scores, should be defined.

Primary Sjögren's syndrome [pSS] is a rare systemic autoimmune disease that chiefly affects middle-aged women (1). Its main pathological feature is a lymphocytic infiltrate of the exocrine glands (mainly salivary and lachrymal), but this inflammatory process often develops beyond this principal target and may affect other organs such as the joints, skin, lung, kidneys, nerves and small vessels. Thus, almost all patients report the same disabling cardinal symptoms associated with the glandular involvement (mouth and eyes dryness, fatigue, and diffuse musculoskeletal pain), and a subset of them experience systemic involvement (such as polysynovitis, inflammatory lung disease or neurologic involvement (2–4)), which can be sometimes severe and is associated with an increased risk of lymphoma development (5). These two facets of the disease have major implications for both daily patient care and the design of clinical trials.

To date, no treatment has proven its efficacy to change the course of the disease and improve the symptoms and/or systemic activity of the disease in large randomized controlled trials (RCTs). However, several open-labelled or small randomized controlled studies have suggested that some biological therapies could improve the symptoms in selected groups of patients, at least temporarily (6). Therefore, new larger RCTs in well-defined pSS patients (i.e., patients that are presumed to respond to a particular treatment and not the total pSS population) are warranted to assess the long-term effects of these treatments.

The chief treatment goal in chronic and usually non-life threatening conditions such as pSS is to improve the patient's perceived health-related quality of life [HR-QoL]. HR-QoL is profoundly impaired in pSS (7–15). Therefore, the principal factors governing HR-QoL impairment must be identified so that they can be specifically targeted by therapeutic interventions, in order to improve the patient's everyday experience.

To standardise the evaluation of disease activity in pSS, validated tools were developed recently (16,17). The EULAR SS Patient Reported Index [ESSPRI] measures the

intensity of patient's symptoms and is determined by having the patient score dryness, pain, and fatigue on 0-to-10 numerical scales then computing the mean of the three scores (18).

The EULAR Primary Sjögren's Syndrome Disease Activity Index [ESSDAI] measures systemic disease activity in 12 weighted domains (i.e. organ systems: cutaneous, respiratory, renal, articular, muscular, PNS, CNS, haematological, glandular, constitutional, lymphadenopathy, biological), with a final score ranging theoretically between 0 and 123 (19,20). Low, moderate, and high systemic activity levels were recently defined as an ESSDAI <5, between 5 and 13, and ≥ 14 , respectively (21).

The objective of this study was to determine associations linking indicators of pSS severity, including the ESSPRI and ESSDAI, to HR-QoL impairments in a selected population of participants in a large prospective therapeutic trial.

PATIENTS AND METHODS

Patients included in the TEARS trial

We analysed baseline data [inclusion visit] from the Tolerance and Efficacy of Rituximab in pSS [TEARS] trial (22) conducted in 120 patients aged 18 to 80 years. Inclusion criteria were American-European Consensus Group classification criteria fulfilment; active disease defined as scores of 50 mm or more on at least two of four 0-100 visual analogue scales [VASs] for global disease, pain, fatigue, and dryness, respectively; and either recent [less than 10 years] and biologically active pSS (presence of autoantibodies [anti-Ro-SSA antibodies or rheumatoid factor], cryoglobulinemia, hypergammaglobulinemia, beta 2-microglobulin elevation, or hypocomplementemia) or systemic pSS with at least one extra-glandular manifestation. Secondary SS patients were excluded. The trial was approved by the appropriate ethics committee [CPP Ouest VI, #2007/493] and registered on clinicaltrials.gov [NCT00740948].

Data collection

The following variables were collected: demographic data [gender, age, body mass index (BMI, overweight defined as BMI>25 kg/m²), and disease duration], patient-reported outcomes [0-100 VASs for global disease activity, limb pain, fatigue, and global, oral and ocular, dryness; and ESSPRI], objective measurements [Schirmer's test ≤ 5 mm/5 min, unstimulated whole salivary flow ≤ 0.1 mL/min, abnormal salivary gland biopsy defined as a focus score (FS) ≥ 1 , and presence of anti-SSA/SSB autoantibodies], and systemic activity assessed by the physician [0-100 VAS for systemic disease activity and ESSDAI].

Patients completed the validated French version of the SF-36, a widely used tool for assessing health-related HR-QoL. Two summary scores are usually analysed, the Physical Component Summary [PCS] and the Mental Component Summary [MCS] scores. Lower PCS and MCS scores indicate a worst HR-QoL. PCS and MCS may vary between 0 and 100 and are normalized to be around 50 in a normal female population (23). The SF-36 can also be assessed using 8 domains, which represent respectively Physical Functioning, Physical role, Bodily pain, Mental Health, Emotional role, Social Functioning, Vitality and General Health. Each of these domains also has values comprised between 0 and 100, with lower values indicating worst QoL.

Statistical analysis

Patients in the different systemic activity level groups were compared using ANOVA or Pearson's Chi² test as appropriate. The correlation between different quantitative variables was assessed using Spearman's test and visualized drawing dispersion plots. The variables associated with PCS and MCS scores were assessed by univariate linear regression. All variables associated with the PCS and/or MCS scores with $p < 0.2$ by univariate analysis were

entered into multivariate linear regression models. The ESSPRI was excluded from the first multivariate model to avoid collinearity, since its value depends entirely on other variables potentially included in the model [mean of pain, fatigue, and dryness VAS scores]. In the second multivariate model, the ESSPRI was included as a surrogate for all other patient-reported outcomes. These analyses were conducted on the total population then on the subpopulation with moderate-to-high systemic activity [ESSDAI \geq 5], since the relative importance of systemic activity as a determinant of HR-QoL cannot be assessed in patients without extra-glandular involvement. All statistical analyses were performed using SPSS [Version 20.0. SPSS Inc., Chicago, IL, USA].

RESULTS

Study patients

Table 1 reports the patient characteristics at inclusion in the TEARS trial, according to their level of systemic activity as defined by the ESSDAI. The general characteristics were similar across the three activity-level groups. Symptom intensity, as assessed by the ESSPRI, was greater in patients with higher systemic disease activity, due to higher pain and fatigue scores without higher dryness scores. Dryness scores were similar across the systemic activity groups, and rather higher than pain and fatigue scores. ESSDAI and ESSPRI scores displayed a moderate but significant correlation (Figure 1). PCS and MCS were not correlated. The PCS score was significantly higher in the patient subgroup with no or low systemic activity compared to patients with moderate and high systemic activity, indicating better perceived physical health, but the MCS score was similar in the three groups.

Determinants of the Physical Component Summary [PCS] score of the SF36

By univariate analysis [Table 2], higher values of most symptom VAS scores were associated with worse PCS scores, but the association was stronger for the ESSPRI than for any single VAS score (Figure 1). Of note, the oral dryness VAS score but not the global or ocular dryness VAS scores was associated with PCS, suggesting that these symptoms should be assessed separately from the ESSPRI. Systemic activity level was moderately associated with the PCS score when assessed using the ESSDAI (Figure 1) but not using the physician's judgement. By multivariate analyses, only patient-reported symptoms were associated with greater HR-QoL impairment and, again, the association was strongest for the ESSPRI. When considering single symptoms, only pain was independently associated with a low PCS; fatigue and dryness were not. The results were similar in the patient subgroup with moderate-to-high systemic activity [Table S1].

Determinants of the Mental Component Summary [MCS] score of the SF36

By univariate analysis, older age was associated with higher MCS scores, whereas higher ESSPRI and pain and fatigue VAS score values were associated with lower MCS scores. Systemic activity level was not associated with the MCS score [Table 3]. By multivariate analysis, only the ESSPRI was associated with a lower MCS score. In the patient subgroup with moderate-to-high systemic activity [Table S2], the ocular dryness VAS score was also associated with a low MCS, but the link was considerably weaker than with the ESSPRI. The systemic activity level was not associated with the MCS. Interestingly, older age was associated with better MCS scores.

Correlations of ESSDAI, ESSPRI and symptoms with individual SF36 domains

Table 4 shows the values of the Spearman's correlation coefficients between each of the eight SF36 domains and ESSPRI, ESSDAI and the different VAS. The ESSDAI was

only moderately correlated with the physical functioning domain of the SF36. The ESSPRI was strongly correlated with all 8 domains of the SF36. Among individual symptom VAS, pain and fatigue were correlated with most of the domains, whereas dryness VAS was only moderately correlated with the social functioning and general health domains. Interestingly, oral dryness but not ocular dryness VAS was also correlated with physical functioning and bodily pain domains.

Expectations of the patients participating in the TEARS trial

Patients were asked at study inclusion to indicate the main symptom they would like to be improved by the study medication. Among the 120 patients, 43 (36%) designated pain, 37 (31%) fatigue, and 37 (31%) dryness. Among the different sites of dryness, they also were asked to indicate which the worst symptom was: 49 (41%) indicated oral dryness, 45 (38%) ocular dryness, 14 (12%) skin dryness, 6 (5%) trachea dryness, and 3 (2%) vaginal dryness.

DISCUSSION

This study is the first to show that patient-reported symptoms, but not the level of systemic activity, are associated with greater HR-QoL impairments in selected patients with active pSS, including those who have a moderate-to-high level of systemic activity. These findings indicate that primary endpoints for therapeutic trials should include the cardinal pSS symptoms [dryness, fatigue, and limb pain], assessed using validated tools such as the ESSPRI, in addition to extra-glandular involvement, which is the primary endpoint in all ongoing clinical trials in pSS. Importantly, the ESSPRI, but not the ESSDAI, improved with rituximab therapy in post-hoc analyses of TEARS trial data (24).

Among these cardinal symptoms, pain seemed to show the strongest association with HR-QoL. However, dryness scores were rather higher than fatigue and pain VASs, irrespective of the systemic activity level, as shown in table 1. Therefore, most patients included in this study had high level of dryness, which may hide an important contribution of this symptom to their altered HR-QoL.

In previous multivariate analyses, the strongest factors associated with HR-QoL impairment were pain, depression, anxiety, and fatigue (9,10,12,13). Our study adds important new findings. First, all previous studies included unselected consecutive patients seen at a single centre (10,12), patients included in a large national cohort (13), or patients selected by a panel of physicians (9). Many patients with pSS have mild and benign disease and are not candidates for the biological therapies currently evaluated in clinical trials (6). HR-QoL impairments were particularly severe in our population: the mean SF36 PCS and MCS scores were 36 ± 9 and 37 ± 10 , respectively, compared to 46 ± 1 and 43 ± 1 (12) and 53 ± 24 and 64 ± 21 (10) in two other studies. Second, the TEARS patients had high systemic activity, with a mean baseline ESSDAI of 10 compared to only 3 in other studies (12,14), which were therefore unable to provide conclusive information about the impact of extra-glandular involvement on HR-QoL. Here, we showed that, even in patients with the highest systemic activity, the strongest factors associated with HR-QoL were patient-reported symptoms. Patients with high systemic activity had a lower PCS score, but multivariate analyses indicated that this observation was explained by the fact that they also had more intense symptoms compared to patients with low systemic activity level. Third, we obtained reliable assessments by using two recently validated standardised tools, the ESSPRI and the ESSDAI. Associations linking these indices to HR-QoL have been assessed in only two previous studies (12,14). Last, we assessed only pSS-related features, whereas other studies included non-specific potential determinants of HR-QoL such as socio-professional factors

and associated conditions, for instance depression. However, neither unemployment nor depression are direct symptoms of pSS, and neither would be used as an endpoint in clinical trials. They rather represent consequences of the disease and its associated HR-QoL impairment, but do not explain this low HR-QoL. Whether these associated conditions could precede the onset of pSS is difficult to assess, but some studies suggested for example that sleep disorders requiring treatment could be more frequent in patients who later develop pSS compared to patients who did not develop pSS (25). Nevertheless, the importance of these factors on HR-QoL is probably major, and these associated conditions have to be taken into account in clinical practice when taking care of individual patients, and may warrant specific therapies besides treatments for pSS-related symptoms.

Our results also suggest that generic tools to assess HR-QoL such as the SF36 probably do not account for the totality of patients' preferences, since there is a discrepancy between the most important symptom to be improved in the opinion of the patient (fatigue or dryness for two thirds of the patients) and the results of our multivariate analysis (putting emphasis on the weight of pain in SF36 score prediction).

To conclude, this study of data from the largest therapeutic trial in pSS published to date demonstrates that patient-reported symptoms, best assessed using the standardised ESSPRI, are stronger predictors of impaired HR-QoL than systemic activity of the disease, assessed by the physician using the ESSDAI. Therefore, future therapeutic trials should focus on these symptoms in addition to systemic disease activity. The choice of the primary endpoint should be made according to the goal of the study and the target population, which are major determinants of the characteristics and feasibility of a trial (26,27). Predictive factors of response should be defined for the different drugs studied, and could include general characteristics of the patients but also objective tools such as salivary gland biopsy (28–30) or major salivary gland ultrasonography (31). Studies aiming at improving well-

being in all patients with pSS should target patient-reported outcomes as primary endpoint, using variation of the ESSPRI or composite criteria such as the recently developed Sjögren's Syndrome Responder Index (24), whereas studies including patients with selected systemic involvement should use variation of the ESSDAI or of one of its subscale as primary endpoint (21). New data-driven consensual response criteria should be designed by reanalysing the data of all clinical trials completed to date in pSS, in order to determine which outcome measures are sensitive to change and would be susceptible to detect a treatment efficacy in future trials.

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Table 1. Characteristics of the patients included in the TEARS trial according to the level of systemic disease activity

		Total population N=120	Low systemic activity N=29	Moderate systemic activity N=57	High systemic activity N=34	<i>p</i> value
General characteristics	Males	8 (7%)	3 (10%)	4 (7%)	1 (3%)	-
	Age [years]	54.2 (13.4)	56.2 (10.9)	52.4 (13.5)	55.4 (15.1)	0.497
	BMI>25 kg/m ²	46 (38%)	11 (38%)	24 (42%)	11 (32%)	0.651
	Disease duration [years]	5.0 (5.7)	4.0 (4.7)	4.4 (4.2)	6.9 (7.9)	0.073
PROs	ESSPRI	64.2 (16.4)	57.6 (14.7)	64.5 (16.6)	69.4 (15.7)	0.015
	Global activity VAS	69.1 (16.2)	65.1 (15.3)	68.3 (15.5)	74.0 (17.4)	0.079
	Pain VAS	53.4 (28.3)	40.5 (29.0)	55.1 (27.6)	61.5 (25.7)	0.010
	Fatigue VAS	69.0 (18.7)	63.7 (19.0)	67.9 (20.0)	75.2 (14.6)	0.043
	Global dryness VAS	70.3 (20.9)	68.5 (18.2)	70.6 (20.8)	71.5 (23.5)	0.841
	Oral dryness VAS	67.7 (24.2)	64.0 (21.0)	69.9 (23.5)	67.0 (28.0)	0.581
	Ocular dryness VAS	61.0 (28.4)	65.4 (22.8)	59.6 (31.2)	59.8 (28.1)	0.659
Objective tests	Schirmer's test ≤5 mm	76 (63%)	16 (55%)	40 (70%)	20 (59%)	0.354
	UWSF ≤0.01 mL/min	76 (63%)	20 (69%)	31 (54%)	25 (74%)	0.123
	Abnormal SG biopsy	106 (88%)	27 (93%)	48 (84%)	30 (88%)	-
	Anti-SSA/SSB	97 (81%)	25 (86%)	47 (82%)	25 (74%)	0.405
Systemic activity	Physician VAS	37.9 (28.4)	25.2 (25.1)	37.4 (27.3)	49.1 (28.9)	0.004
	ESSDAI	10.1 (6.8)	3.1 (1.1)	8.1 (2.4)	19.4 (4.5)	<0.001
HR-QoL (SF36)	PCS	36.3 (9.1)	40.8 (7.7)	36.0 (9.2)	33.0 (8.9)	0.004
	MCS	36.5 (9.6)	34.8 (8.5)	37.2 (10.0)	36.7 (9.9)	0.582

Systemic activity levels were defined according to the ESSDAI, as follows: 0-4, low; 5-13, moderate; and ≥14, high. The *p* values are for the comparison of the three groups [ANOVA or Pearson Chi² test as appropriate]. Categorical data are n (%) and continuous data mean (standard deviation).

BMI, body mass index; PRO, patient-reported outcome; ESSPRI, EULAR Sjogren's Syndrome Patient Reported Index; VAS, visual analogue scale; UWSF, whole unstimulated salivary flow; SG, salivary gland; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; HR-QoL, quality of life; PCS, SF36 physical component summary score; MCS, SF36 mental component summary score

Table 2. Determinants of the SF36 Physical Component Summary [PCS] score

		Univariate		Multivariate model 1		Multivariate model 2	
		Beta	<i>p</i> value	Beta	<i>p</i> value	Beta	<i>p</i> value
General characteristics	Male gender	2.963	0.410				
	Age [years]	-0.017	0.792				
	BMI>25 kg/m ²	-3.917	0.027	-1.661	0.249	-2.217	0.143
	Disease duration [years]	-0.247	0.102				
PROs	ESSPRI	-0.301	<0.001	N/A		-0.263	<0.001
	Global VAS	-0.170	0.001	0.015	0.763	N/A	
	Pain VAS	-0.191	<0.001	-0.150	<0.001	N/A	
	Fatigue VAS	-0.196	<0.001	-0.069	0.105	N/A	
	Global dryness VAS	-0.053	0.215				
	Oral dryness VAS	-0.092	0.011	-0.025	0.444	N/A	
	Ocular dryness VAS	-0.058	0.059	-0.041	0.124	N/A	
Objective tests	Schirmer's test ≤5 mm	0.287	0.873				
	UWSF ≤0.01 mL/min	3.32	0.064	1.481	0.333	1.998	0.20
	Abnormal SG biopsy	-0.038	0.988				
	Anti-SSA/SSB	0.307	0.889				
Systemic activity	Physician VAS	-0.036	0.239				
	ESSDAI	-0.335	0.007	-0.161	0.128	-0.185	0.10

Categorical data are n (%) and continuous data mean (standard deviation). Univariate analysis was performed using linear regression (beta value), and variables associated with the PCS score at $p < 0.2$ by univariate analysis were entered into multivariate linear regression models. In model 1, each PRO scale was considered independently, whereas in model 2 the ESSPRI was used as a summary of all other PRO scales.

BMI, body mass index; PRO, patient-reported outcome; ESSPRI, EULAR Sjogren's Syndrome Patient Reported Index; VAS, visual analogue scale; UWSF, whole unstimulated salivary flow; SG, salivary gland; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index

Table 3. Determinants of the SF36 Mental Component Summary [MCS] score

		Univariate		Multivariate model 1		Multivariate Model 2	
		Beta	P	Beta	P	Beta	P
General characteristics	Male gender	-1.82	0.629				
	Age (years)	0.143	0.037	0.096	0.157	0.102	0.129
	BMI>25	-1.867	0.317				
	Disease duration [years]	0.106	0.504				
PROs	ESSPRI	-0.183	0.001	N/A		-0.159	0.004
	Global VAS	-0.163	0.003	-0.058	0.345	N/A	
	Pain VAS	-0.089	0.005	-0.034	0.346	N/A	
	Fatigue VAS	-0.165	<0.001	-0.09	0.093	N/A	
	Global dryness VAS	-0.048	0.291				
	Oral dryness VAS	-0.004	0.921				
	Ocular dryness VAS	-0.06	0.06	-0.056	0.074	N/A	
Objective tests	Schirmer's test ≤ 5 mm	-1.885	0.318				
	UWSF ≤ 0.01 mL/min	2.836	0.132	1.839	0.318	1.775	0.330
	Abnormal SG biopsy	-2.325	0.399				
	Anti-SSA/SSB	2.707	0.237				
Systemic activity	Physician VAS	-0.026	0.414				
	ESSDAI	0.092	0.491				

Categorical data are n (%) and continuous data mean (standard deviation). Univariate analysis was performed using linear regression (beta value), and variables associated with the MCS score at $p < 0.2$ by univariate analysis were entered into multivariate linear regression models. In model 1, each PRO scale was considered independently, whereas in model 2 the ESSPRI was used as a summary of all other PRO scales.

BMI, body mass index; PRO, patient-reported outcome; ESSPRI, EULAR Sjogren's Syndrome Patient Reported Index; VAS, visual analogue scale; UWSF, whole unstimulated salivary flow; SG, salivary gland; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index

Table 4. Correlations of ESSDAI, ESSPRI, and pSS symptoms with individual domains of the SF36

		Physical Functioning	Physical role	Bodily pain	Mental Health	Emotionnal role	Social Functioning	Vitality	General Health
ESSDAI	Rho	-0.247	-0.170	-0.159	0.031	-0.082	0.055	-0.149	-0.141
	P	0.008	0.068	0.089	0.737	0.382	0.557	0.108	0.132
ESSPRI	Rho	-0.401	-0.384	-0.611	-0.327	-0.287	-0.498	-0.467	-0.431
	P	<0.001	<0.001	<0.001	<0.001	0.002	<0.001	<0.001	<0.001
Global VAS	Rho	-0.298	-0.270	-0.396	-0.186	-0.248	-0.363	-0.268	-0.285
	P	0.001	0.003	<0.001	0.044	0.007	<0.001	0.004	0.002
Pain VAS	Rho	-0.438	-0.446	-0.703	-0.292	-0.324	-0.403	-0.413	-0.352
	P	<0.001	<0.001	<0.001	0.001	<0.001	<0.001	<0.001	<0.001
Fatigue VAS	Rho	-0.300	-0.286	-0.415	-0.341	-0.128	-0.421	-0.530	-0.352
	P	0.001	0.002	<0.001	<0.001	0.173	<0.001	<0.001	<0.001
Dryness VAS	Rho	-0.051	-0.001	-0.117	0.002	-0.089	-0.219	-0.060	-0.212
	P	0.587	0.989	0.212	0.985	0.343	0.018	0.522	0.022
Oral dryness VAS	Rho	-0.237	-0.056	-0.204	0.013	-0.051	-0.195	-0.113	-0.187
	P	0.011	0.551	0.029	0.888	0.589	0.036	0.228	0.045
Ocular dryness VAS	Rho	-0.127	-0.138	-0.126	-0.143	-0.136	-0.280	-0.164	-0.264
	P	0.179	0.141	0.180	0.126	0.147	0.002	0.079	0.004

ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjogren's Syndrome Patient Reported Index; VAS, visual analogue scale; Rho: Spearman's correlation coefficient.

Table S1. Determinants of the SF36 Physical Component Summary [PCS] score in patients with moderate systemic activity [ESSDAI \geq 5]

		Univariate		Multivariate model 1		Multivariate model 2	
		Beta	<i>p</i> value	Beta	<i>p</i> value	Beta	<i>p</i> value
General characteristics	Male gender	6.961	0.178	3.839	0.441	3.204	0.522
	Age [years]	-0.63	0.384				
	BMI>25 kg/m ²	-3.451	0.086	-2.46	0.185	-3.137	0.095
	Disease duration [years]	-0.224	0.161	-0.130	0.360	-0.151	0.296
PROs	ESSPRI	-0.241	<0.001	N/A		-0.201	0.001
	Global VAS	-0.135	0.02	0.007	0.912	N/A	
	Pain VAS	-0.173	<0.001	-0.132	0.001	N/A	
	Fatigue VAS	-0.158	0.002	-0.040	0.462	N/A	
	Global dryness VAS	-0.035	0.439				
	Oral dryness VAS	-0.064	0.099	-0.012	0.764	N/A	
	Ocular dryness VAS	-0.072	0.029	-0.046	0.153	N/A	
Objective tests	Schirmer's test \leq 5 mm	0.557	0.784				
	UWSF \leq 0.01 mL/min	3.216	0.107	2.36	0.214	2.64	0.149
	Abnormal SG biopsy	0.794	0.774				
	Anti-SSA/SSB	-2.507	0.286				
Systemic activity	Physician VAS	0.011	0.748				
	ESSDAI	-0.266	0.081	-0.139	0.319	-0.163	0.250

Categorical data are n (%) and continuous data mean (standard deviation). Univariate analysis was performed using linear regression (beta value), and variables associated with the PCS score at $p < 0.2$ by univariate analysis were entered into multivariate linear regression models. In model 1, each PRO scale was considered independently, whereas in model 2 the ESSPRI was used as a summary of all other PRO scales.

BMI, body mass index; PRO, patient-reported outcome; ESSPRI, EULAR Sjogren's Syndrome Patient Reported Index; VAS, visual analogue scale; UWSF, whole unstimulated salivary flow; SG, salivary gland; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index.

Table S2. Multivariate analysis of determinants of the SF36 Mental Component Summary [MCS] score in patients with moderate systemic activity [ESSDAI \geq 5]

		Univariate		Multivariate model 1		Multivariate model 2	
		Beta	<i>p</i> value	Beta	<i>p</i> value	Beta	<i>p</i> value
General characteristics	Male gender	3.001	0.604				
	Age [years]	0.196	0.014	0.131	0.079	0.152	0.043
	BMI>25 kg/m ²	-0.128	0.955				
	Disease duration [years]	0.149	0.404				
PROs	ESSPRI	-0.232	<0.001	N/A		-0.211	0.001
	Global VAS	-0.28	<0.001	-0.127	0.086	N/A	
	Pain VAS	-0.118	0.003	-0.047	0.268	N/A	
	Fatigue VAS	-0.196	<0.001	-0.098	0.096	N/A	
	Global dryness VAS	-0.076	0.135	0.062	0.277	N/A	
	Oral dryness VAS	-0.026	0.551				
	Ocular dryness VAS	-0.082	0.024	-0.084	0.030	N/A	
Objective tests	Schirmer's test \leq 5 mm	-0.784	0.732				
	UWSF \leq 0.01 mL/min	1.832	0.413				
	Abnormal SG biopsy	-3.351	0.274				
	Anti-SSA/SSB	0.807	0.758				
Systemic activity	Physician VAS	-0.021	0.581				
	ESSDAI	0.017	0.919				

Categorical data are n (%) and continuous data mean (standard deviation). Univariate analysis was performed using linear regression (beta value), and variables associated with the MCS score at $p < 0.2$ by univariate analysis were entered into multivariate linear regression models. In model 1, each PRO scale was considered independently, whereas in model 2 the ESSPRI was used as a summary of all other PRO scales.

BMI, body mass index; PRO, patient-reported outcome; ESSPRI, EULAR Sjogren's Syndrome Patient Reported Index; VAS, visual analogue scale; UWSF, whole unstimulated salivary flow; SG, salivary gland; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index.

Figure 1: Dispersion plots and Spearman's correlation analysis between PCS, MCS, ESSPRI and ESSDAI scores

