Factors influencing the EULAR Sjögren's Syndrome Patient-Reported Index in primary Sjögren's syndrome

M.G. Sandoval-Flores, I. Chan-Campos, G. Hernández-Molina

Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

Maria Graciela Sandoval-Flores, MD
Isela Chan-Campos, MD
Gabriela Hernández-Molina, MS

Please address correspondence to:
Gabriela Hernández-Molina,
Department of Immunology and Rheumatology,
Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán,
Vasco de Quiroga 15,
Col. Belisario Domínguez Sección XVI,
CP 14080, Mexico City, Mexico.
E-mail: gabyhm@yahoo.com

ORCID 001-7958-0391

Received on March 13, 2021; accepted in revised form on June 7, 2021.

Clin Exp Rheumatol 2021; 39 (Suppl. 133: S153-S158.

Key words: Sjögren's syndrome, ESSPRI, variation, sicca symptoms, pain, fatigue

Competing interests: none declared.

ABSTRACT

Objective. *The EULAR Sjögren's Syndrome Patient-Reported Index (ESSPRI) is a validated tool for measuring pain, fatigue and dryness in primary Sjögren's syndrome (pSS). We evaluated its association with disease and non-disease related variables, and its variation though the follow-up.*

Methods. *We included 130 pSS patients who were interviewed to register demographics, schooling, smoking, menopause, body mass index, disease duration, use of hormonal replacement, associated sicca drugs, prednisone, immunosuppressors/antimalarials, comorbidities such as diabetes mellitus, hypothyroidism, depression, fibromyalgia and scored the Charlson comorbidity index. We assessed the non-stimulated whole salivary flow (NSWSF), Schirmer-I test, ESSDAI and ESSPRI scores. In a subset of patients, we scored a second ESSPRI.*

Results. *Most patients were women, mean age 57 years and median disease duration 9.3 years. The median ESSPRI score was 6 (fatigue 6, pain 4, dryness 8). Eighty patients (61.5%) had an ESSPRI ≥5 points and were characterised by a higher prevalence of depression (OR 3.7, 95% 1.2–11.3) and lower NSWSF (OR 0.59, 95% CI 0.36–0.97). Among 62 patients with a second ESSPRI (median time 25 months), 44 (70%) experienced a decrement/increment ≥1 in the ESSPRI (16 were decrement). We did not find any of the studied variables associated with this variation, also including change in prednisone or immunosuppressors.*

Conclusion. *An ESSPRI ≥5 (unsatisfactory symptom state) was associated with low NSWSF and depression. Most of the patients experienced a clinically significant ESSPRI variation (increment or decrement), nevertheless, we were not able to identify any variable associated with this change. Further studies would be helpful to understand the underlying causes.*

Introduction

Sjögren's syndrome (SS) is an autoimmune chronic disease characterised by dysfunction and destruction of salivary and lacrimal glands associated with a wide spectrum of systemic manifestations. Dryness, fatigue and pain are symptoms frequently seen in patients with primary Sjögren's syndrome (pSS) and impact their quality of life (QoL) (1). Oral and ocular dryness are present in almost all of the patients (2, 3), whereas fatigue in half of them (4). In the United Kingdom pSS registry, both physical and mental fatigue were associated with depression and daytime sleepiness; and 40% of the patients graded fatigue as the symptom with an improvement need (5). On the other hand, in French pSS population, pain was present in 18.1% of the patients (6). Moreover, these symptoms might be related between them. For instance, a study reported as fatigue predictors, the presence of depression and pain (7). Cluster analysis and symptom stratification based on patient-reported outcomes (PRO), have also helped to identify subgroups of SS (*i.e.* low symptom burden, high symptom burden and dryness dominant with fatigue, etc.) that might have different organ involvement and burden of illness (8-9).

The EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) is a validated index that measures these three cardinal symptoms using 0-10 numerical scales, and the final score is the mean of the scores of each domain. This tool has showed good correlation with the both the global patient's and physician's assessment, the PROFAD score, the SS symptoms inventory and the EVA pain scale (10-11). In addition, a higher ESSPRI score implies worst QoL and a negative impact in disease

burden (12-14), but not higher systemic activity (10, 15). Indeed, in order to have a complete "picture" of SS; it is recommended to evaluate patients using, both a disease activity instrument (ESSDAI) (10) and a patient's reported outcome such as the ESSPRI (16).

Moreover, a study that evaluated parotid ultrasonographic changes in SS patients, described higher scores of the dryness domain of the ESSPRI among patients with more severe parotid ultrasonographic changes. Nevertheless, this finding was not true for the global ESSPRI score as well as the rest of its domains (17).

Nowadays, the ESSPRI has been widely used in randomised clinical trials (RCT) as the main PRO for SS; however longitudinal data derived from the real clinical setting is scarce. Up to date, only a study described that the ESSPRI remained stationary at a median follow-up of 3 years in a cohort of Korean pSS patients (18). Furthermore, it is unknown if the ESSPRI (both basal or at follow-up), might be influenced by diverse variables. Thus, in the present work we evaluated the association of the ESSPRI with demographics, SS related and non-SS related variables. Moreover, we assessed its behaviour during the follow-up in our cohort of pSS patients.

Table I. Clinical features according to ESSPRI status.

Variable	All cohort n=130	ESSPRI ≥5 n=80	ESSPRI <5 n=50	*p*
Women, n (%)	128 (98.4)	80 (100)	48 (96)	0.14
Age in years, mean ± SD	57.1 ± 13.4	56.3 ± 12.8	54.7 ± 0.92	0.49
Body mass index in kg/m^2, mean ± SD	25.2 ± 5.6	25.4 ± 4.6	24.4 ± 5.3	0.31
Median years of disease, (IQR)	9.3 (3.5-14.9)	10.3 (3.6-16.9)	8.7 (2.2-12.04)	0.85
Schirmer <5 mm/5 min, n (%)	110 (84.6)	68 (85)	43 (86)	0.72
Keratoconjunctivis sicca, n (%)	51/76 (67.1)	33/47 (70.2)	18/29 (62)	0.75
Median NSWSF in ml/15 min	0.5 (0.1-1)	0.2 (0.1-0.77)	0.5 (0.1-1)	0.05
MSGB with focus score ≥1, n (%)	90 (69.2)	60 (75)	30 (60)	0.11
Median basal ESSDAI (IQR)	2 (0-3)	2 (0-3)	1 (0-2.7)	0.76
Antinuclear antibodies, n (%)	103/127 (81.1)	64/77 (83.1)	39 (78)	0.40
Rheumatoid factor, n (%)	75/129 (58.1)	51/80 (63.7)	24/49 (48.9)	0.06
Anti-Ro/SSA, n (%)	112 (86)	69 (86.2)	43 (86)	1
Anti-La/SSB, n (%)	60 (46.1)	37 (46.2)	23 (46)	0.9
Low C3, n (%)	75/129 (58.1)	51/80 (63.7)	24/49 (48.9)	0.50
Low C4, n (%)	27/111 (24.3)	16/70 (22.8)	11/41 (26.8)	0.68
Current use of immunosuppressor/antimalarial, n (%)	74 (56.9)	47 (58.5)	27 (54)	0.45
Current use of glucocorticoids, n (%)	20 (15.3)	13 (16.3)	7 (14)	0.72
Current smoking, n (%)	10 (7.8)	7 (8.8)	3 (6.0)	0.56
Smoking history, n (%)	46 (35.3)	30 (37.5)	16 (32.0)	0.57
Menopause, n (%)	93 (71.5)	60 (75.0)	33 (66.0)	0.26
Hypothyroidism, n (%)	41 (31.5)	28 (35)	13 (26)	0.28
Fibromyalgia, n (%)	11 (8.4)	10 (12.5)	1 (2)	0.05
Depression, n (%)	29 (22.3)	24 (30)	5 (10)	0.008
Diabetes mellitus, n (%)	13 (0.1)	9 (11.3)	4 (8)	0.54
Median Charlson Index (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0.91
Current use of drugs associated with dryness, n (%)	31 (23.8)	21 (26.3)	10 (20)	0.41
Hormonal replacement, n (%)	18 (13.8)	11 (13.8)	7 (14)	0.96
Schooling level, n (%)				0.66
Elementary	33 (25.3)	20 (25)	13 (26)	
Mild school	35 (26.9)	20 (25)	15 (30)	
High school	31 (23.8)	21 (26.3)	10 (20)	
College	31 (23.8)	19 (23.8)	12 (24)	
Season of the year, n (%)				0.37
Spring	27 (20.7)	17 (21.3)	10 (20)	
Summer	14 (10.7)	7 (8.8)	7 (14)	
Fall	68 (52.3)	45 (56.3)	23 (46)	
Winter	21 (16.1)	11 (13.8)	10 (20)	

NSWSF: non-stimulated whole salivary flow; ESSDAI: EULAR Sjögren's syndrome disease activity; MSGB: minor salivary gland biopsy.

Methods

This study was performed in a third level referral centre for rheumatologic patients. We included 103 consecutive patients with pSS according to the ACR/EULAR classification criteria (19). We excluded patients with another concomitant connective disease.

A single rheumatologist had a face-to-face interview with the patient and registered the following variables: demographics, schooling level, smoking (current and history), menopause and disease duration. Moreover, we asked about the current use of hormonal replacement, as well as the most frequently drugs associated with dry mouth such as diuretics, anticholinergics, antihistamines, antidepressants, and ACE inhibitors (20).

We also registered the use of prednisone, antimalarial and immunosuppressors. We also obtained from the medical chart, some clinical and serological SS variables, the presence of comorbidities such as diabetes mellitus, hypothyroidism, depression, and fibromyalgia. We scored the Charlson comorbidity index (21) and the ESSDAI (10).

We evaluated the Schirmer-I test and the non-stimulated whole salivary flow (NSWSF). Both tests were performed during the morning and in a closed room with no air conditioning or heating. In order to measure the NSWSF, patients were asked to refrain from eating, drinking, smoking, chewing, or oral hygiene procedures for at least 3 hours before the evaluation. They had to swallow their saliva before the start of the test; and then the saliva was collected for 15 minutes using the spitting method. The volume of saliva was measured after decantation using a calibrated syringe. The volume was considered abnormal if ≤1.5 ml/15 minutes (22).

ESSPRI assessment

Patients scored the ESSPRI index. As for the ESSPRI, the patient satisfactory symptom state has been defined with a cut-off <5 points (12); we compared the characteristics of the patients with an ESSPRI ≥5 (unsatisfactory symptom state) *versus* the group with ESSPRI <5 (satisfactory symptom state).

In a subset of patients we also scored a second ESSPRI within a period of 6-41 months and registered any change in systemic treatment during this time. We compared patients with an ESSPRI change ≥1 point (decrement or increment) vs. the group with an ESSPRI <1 change point (decrement or increment)

Statistical analysis

We used descriptive statistics, χ^2 test, Student t-test, Mann-Whitney U-test and Wilcoxon signed-rank test as appropriated according to distribution of the variables. We used logistic regression analysis reporting OR and 95% CI. A two-tailed $p<0.05$ was considered statistically significant. All analyses were performed using the SPSS.

This study was approved by the Institutional Biomedical Research Board of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico.

Results

We included 130 patients, most of them women (98.4%), with a mean age 57±13.4 y/o and median disease duration of 9.3 years. Table I shows the clinical and serological variables of all the cohort. Ocular and oral sicca symptoms were present in 93.8% and 88.4%, respectively. The median NSWSF was 0.5 ml/15 min and 110 (84.6%) patients had a positive Schirmer-I test. At the moment of the evaluation, 74 patients (56.9%) were under immunosuppressors/antimalarials and 20 (15.3%) patients used prednisone.

ESSPRI

The median ESSPRI score was 6 points (fatigue=6 points, pain=4 points and dryness=8 points). Eighty patients (61.5%) had an ESSPRI score ≥5 points. When we compared this group *versus* the group with an ESSPRI <5 (n=50) (Table I), the groups were similar in age, disease duration, prevalence of Schirmer's test, ESSDAI score, use of immunosuppressors/antimalarials and glucocorticoids. Also, the frequency of current smoking, menopause, hypothyroidism, diabetes mellitus and the Charlson index was similar among the groups. In addition, we did not find differences regarding the current use of drugs associated with dryness, hormonal replacement, schooling level and season of the year. However, the ESSPRI ≥5 group had a lower NSWSF, a higher prevalence of fibromyalgia (12.5% *vs*. 2%) and depression (30% *vs*. 10%).

The frequency of serological factors such as RF, ANA, anti-Ro/SSA, anti-La/SSB antibody and low C3 or C4 was also similar among the groups.

At the logistic regression analysis, that included the variables that were statistically different at the univariate analysis, we observed that the variables that remained associated with an ESSPRI ≥5 were depression OR 3.7 (95%CI 1.23–11.3, p=0.02) and the NSWSF (OR 0.59, 95%CI 0.36–0.97, p=0.03).

In a subset of 62 patients with a second ESSPRI assessment after a median time of 25 months (range 641), the median ESSPRI score was 5.1 points (fatigue=5 points, pain=4 points and dryness=6 points). When we compared the basal and the follow up ESSPRI results, we observed a difference between the overall ESSPRI score, the fatigue and dryness domains, but not in the pain domain (Table II).

Among these 62 patients, we identified 44 (70%) of them who changed their ESSPRI ≥1 point and 18 (29.9%) who did not. Table III shows the comparison of these groups regarding demographics, related and non-related SS variables. We did not observe any significant difference among them, including the variable change in prednisone or immunosuppressor/antimalarial treatment.

Table II. Basal and follow-up ESSPRI results.

	Basal ESSPRI	Follow-up ESSPRI	*p*
Median sicca symptoms score (IQR)	8 (5-9)	6 (5-8.2)	0.004
Median pain score (IQR)	4 (2-5)	4 (0-7)	0.89
Median fatigue score (IQR)	6 (4-8)	5 (3-8)	0.02
Total	6 (4.2-7.3)	5.1 (3.7-6.7)	0.01

Table III. Differences among patients with change in ESSPRI (increment or decrement).

Variable	Change ≥1 point (increment or decrement) n=44	Change <1 point n=18	*p*
Age in years, mean ± SD	56.1 ± 12.1	58.4 ± 13.9	0.52
Body mass index in kg/m^2, mean ± SD	23.8 ± 5.8	24.5 ± 5.1	0.4
Median years of disease, (IQR)	9.9 (4.5-12.7)	10.6 (3.9-9.9)	0.6
Median NSWSF in ml/15 min (IQR)	0.5 (0.1-1)	0.2 (0-1)	0.78
Median follow-up ESDDAI (IQR)	1 (0.2-2.7)	1.5 (0-4.2)	0.30
Change in prednisone or immunosuppressors/antimalaria, n (%)	21 (47.7)	9 (50)	0.87
Current smoking, n (%)	2 4.5)	2 (11.1)	0.37
Smoking history, n (%)	16 (36.4)	7 (38.8)	0.85
Menopause, n (%)	32 (72.7)	13 (72.2)	0.96
Hypothyroidism, n (%)	9 (20.5)	7 (38.8)	0.13
Fibromyalgia, n (%)	4 (9.1)	2 (11.1)	1
Depression, n (%)	11 (25)	5 (27.7)	0.82
Diabetes mellitus n (%)	7 (15.9)	3 (16.7)	0.94
Median Charlson Index (IQR)	0 (0-1.2)	0.5 (0-1)	0.48
Current use of drugs associated with dryness, n (%)	13 (29.6)	6 (33.3)	0.77
Hormonal replacement, n (%)	4 (9.1)	1 (5.6)	0.64
Schooling level, n (%)			0.58
Elementary	12 (27.3)	6 (33.3)	
Mild school	14 (31.8)	6 (33.3)	
High school	7 (15.9)	3 (16.7)	
College	11 (25)	11 (25)	
Season of the year, n (%)			0.93
Spring	8 (18.2)	4 (22.2)	
Summer	6 (13.6)	3 (16.7)	
Fall	26 (59.1)	9 (50)	
Winter	4 (9.1)	2 (11.1)	

*NSWSF: non-stimulated whole salivary flow; ESSDAI: EULAR Sjögren's syndrome disease activity.

As a sensitivity analysis, we analysed the group of patients (n=16) with a significant clinical improvement of the ESSPRI (decrement of ≤1 point) and compared with the group without improvement (n=46). We also did not find any difference regarding the previous variables (data not showed). Finally, when comparing the patients (n=28) with clinical worsening of the ESSPRI (increment of ≥1 point) *versus* the group without worsening (n=34), both groups were also similar (data not shown).

Discussion

PROs are important components of patient's assessment in rheumatic diseases. In this sense, in SS the ESSPRI has been widely used in RCT (23). In the present study, our first aim was to identify if there were some variables inherent to SS disease (onset time, disease duration, Schirmer's test, NSWSF, disease treatment, serology) and/or other non-disease related variables (comorbidities, menopause status, other treatments, schooling, ambient factors, etc.) that might influence having an ESSPRI ≥5 (unsatisfactory symptom state).

Previously, Pertovaara *et al*. reported that the ESSPRI score correlated with disease duration, the patient's global assessment, EVA pain scale and QoL. There was also a mild correlation with ESR and β2microglobulin, but not with haemoglobin, leucocytes, platelet count, CRP, immunoglobulin serum levels or complement (C3, C4) (24). In our study, we did not find an association of an ESSPRI ≥5 with any of the SS related variables including age, disease duration and serological variables.

Several studies have described a weak correlation between objective and subjective indices of ocular dryness (16, 25). In contrast, the relationship between oral discomfort and objective oral dryness measures seems to be stronger (25). Herein we observed that patients with an ESSPRI ≥5 had lower NSWSF values. Likewise, another study reported that the sicca domain of the ESSPRI correlated negatively with the NSWSF (r=-0.23) (20) and a former study of our group also described a mild negative correlation with the overall ESSPRI score (τ=-0.26) (21). Recently, Lackner et al. described that patient's perception of dryness assessed by the dryness domain of the Primary Sjögren's syndrome Quality of Life Questionnaire, a disease-specific HRQL questionnaire, correlated with objective measurements of salivary gland function (Schirmer's test r=-0.31 and NSWSF r=-0.35). Albeit, they found no significant correlation with objective dryness tests and the ESSPRI-dryness domain. In addition, they did describe a moderate correlation with the pain and fatigue domains of the ESSPRI, suggesting a more complex relationship (28).

Regarding the non-SS related variables, comorbidity has been reported in 57.1% of SS patients (29), being some of them: cardiovascular disease, malignancy, infections, fibromyalgia and depression (30-31). Herein, we did not observe that the presence of DM, hypothyroidism or others entities assessed by the Charlson index had an association with a satisfactory symptom state. Li *et al*. also reported lack of association with comorbidities (cardiovascular disease, kidney disease, interstitial lung disease and liver disease), DMARDs and disease duration with ocular sicca symptoms; whereas age, education level, disease duration and activity were related with oral symptoms (29).

On the other hand, we initially find an association with the presence of fibromyalgia and depression, remaining only the last one at the multivariate analysis. Fibromyalgia is present in 6.9-55% of pSS patients, and has been linked with constitutional symptoms, fatigue, arthralgias, splenomegaly and dyslipidemia (32). In contrast, depression is present in 8.3–75.5%. Indeed, in a systematic revision of 12 studies including 1917 pSS patients and 1044 controls, pSS was associated with depression with an OR 5.36 95% CI 4.05–7.09) (33). Depression has been related in pSS with fatigue, low QoL, loss of work productivity, high levels of physical disability, higher medical costs, higher ERS, lower educational level, pain and ocular symptoms (33-34). Moreover, a negative correlation with the ESSPRI score (r =–0.26) has been reported (35), a result that goes in agreement with our findings (more depression in the unsatisfactory symptom state group).

Data from the UK Primary Sjögren's Syndrome Registry, showed that when patients were classified depending on the degree of discrepancy between their objective and subjective symptoms classes (stoical, sensitive and accurate), stoical patients (asymptomatic or low symptomatic but with positive objective sicca test) showed significantly less anxiety and depression than the other groups (25).

In the present study, we also evaluated other variables such as menopause, hormonal replacement, use of drugs associated with dryness, schooling and seasonality; and did not find an association with an ESSPRI. Likewise, a study that evaluated the potential seasonality (spring, summer, fall and winter) variation of pain, fatigue and dryness, using visual analogue scales, obtained from patients coming from 3 randomised placebo-control trials (infliximab, hydroxychloroquine and rituximab) in pSS, found no significant changes according to the season (36).

Our second aim was to explore the stability and/or change of the ESSPRI though the time. During the ESSPRI validation, Seror *et al*. reported a low sensitive to change of the instrument, although better than the SSI questionnaire and the PROFAD (11). Up to date, data regarding the change in the ESSPRI derived mainly from clinical trials in biologics, with controversial results. For instance, some have showed a significant clinical improvement (37-38), while others not (39). It is important to highlight that the minimal clinically important improvement is a decrement of at least one point or 15% of the ESSPRI score (23).

In our study, 70% of the patients showed a significant change in the ESSPRI ≥1 point (decrement or increment) during a minimum period of follow-up of 6 months, whereas only 25.8% showed improvement. In contrast, a Korean study of 115 pSS patients reported that the ESSPRI, ClinESSDAI and EQ-5D remained stable during a median 3-year follow-up. Nevertheless, they only evaluated the group with ESSPRI improvement (18). Herein, be-

sides the high variation in the ESSPRI score during the follow-up, we were not able to identify if treatment of any other SS or non-SS related variables were associated with this change (worsening or improvement). It might be possible that is related to other reasons. Recently, a study that enrolled 475 subjects who were screened (using the OSDI score) for Dry eye syndrome (DES), showed that the prevalence of symptomatic DES was higher in women, blue-collar workers, unemployed persons and persons with extremely high BMI (≥30.0 kg/m^2), after adjusting by age, hypertension, diabetes, menopausal status, hormone replacement therapy, occupation, and lifestyle factors (40).

Certainly, our study has some limitations. First, we did not register the use and the intensity of ocular topic treatments that might have impacted our results. On the other way, none of our patients were under cholinergic agonists, as they are not available in our country. Also, although we registered the use of the most frequent drugs associated with xerostomia, it is probably that other factors such as the number of drugs, drugs combination, time of intake and reliability of the patients' report might influence the presence of xerostomia. Second, we were not able to consider all type of comorbidities, but we included the more prevalent in this population. We also did not consider as a comorbidity the presence of osteoarthrosis, nevertheless to score the pain domain of the ESSPRI, we should exclude pain attributed for any other cause besides SS. Third, we did not evaluate NSWSF during the follow-up of the patients, nevertheless objective measures had been shown to be poorly sensitive to change through the time (16). Finally, our results came from a monocentric cohort.

Summing up, we observed that an ESSPRI ≥5 (unsatisfactory symptom state) was associated with low NSWSF and depression. Moreover, most of the patients experienced a clinically significant variation though the follow-up (increment or decrement), nevertheless, we were not able to identify any variable associated with this change. Thus, further studies would be helpful to understand the underlying causes.

References

1. BOMBARDIERI M, ARGYROPOULOU O, FERRO F *et al*.: One year in review 2020: pathogenesis of primary Sjögren's syndrome. *Clin Exp Rheumatol* 2020; 38 (Suppl. 126): S3-9.
2. MANFRÈ V, CAFARO G, I RICCUCCI I *et al*.: One year in review 2020: comorbidities, diagnosis and treatment of primary Sjögren's syndrome. *Clin Exp Rheumatol* 2020; 38 (Suppl. 126): S10-22.
3. SEROR R, RAUZ S, GOSSET M *et al*.: Disease activity and patient reported outcome measures in Sjögren's - what are the best tools to evaluate? *Rheumatology* 2019; Jun 24.
4. GILES I, ISENBERG D: Fatigue in primary Sjögren's syndrome: is there a link with the fibromyalgia syndrome? *Ann Rheum Dis* 2000; 59: 875-8.
5. HACKETT KL, DAVIES K, TARN J *et al*.: Pain and depression are associated with both physical and mental fatigue independently of comorbidities and medications in primary Sjögren's syndrome. *RMD Open* 2019; 24; 5: e000885.
6. CORNEC D, DEVAUCHELLE-PENSEC V, MARIETTE X *et al*.: Severe health-related quality of life impairment in active primary Sjögren's syndrome and patient-reported outcomes: data from a large therapeutic trial. *Arthritis Care Res* 2017; 69: 528-35.
7. SEGAL B, THOMAS W, ROGERS T *et al*.: Prevalence, severity, and predictors of fatigue in subjects with primary Sjögren's syndrome. *Arthritis Rheum* 2008; 59: 1780-7.
8. TARN JR, HOWARD-TRIPP N, LENDREM DW *et al*.: Symptom based stratification of patients with primary Sjögren's syndrome: multi-dimensional characterization of international observational cohorts and reanalyzes of randomized clinical trials. *Lancet Rheumatol* 2019; 1: e85-94.
9. GAIRY K, KNIGHT C, ANTHONY P *et al*.: Burden of illness among subgroups of patients with primary Sjögren's syndrome and systemic involvement. *Rheumatology* 2021; 60: 1871-81.
10. SEROR R, RAVAUD P, MARIETTE X *et al*.: EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI): development of a consensus patient index for primary Sjögren's syndrome. *Ann Rheum Dis* 2011; 70: 968-72.
11. SEROR R, THEANDER E, BRUN JG *et al*.: Validation of EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient indexes (ESSPRI). *Ann Rheum Dis* 2015; 74: 859-66.
12. CHO HJ, YOO JJ, YUN CY *et al*.: The EULAR Sjögren's syndrome patient reported index as an independent determinant of health-related quality of life in primary Sjögren's syndrome patients: in comparison with non-Sjögren's sicca patients. *Rheumatology* 2013; 52: 2208-17.
13. LEE J, KOH JH, KWOK SK *et al*.: The EULAR Sjögren's Syndrome Patient-Reported Index is an independent determinant of health-related utility values of Korean patients with primary Sjögren's syndrome. *Clin Exp Rheumatol* 2016; 34: 663-7.
14. LENDREM D, MITCHELL S, McMEEKIN P *et al*.: Do the EULAR Sjögren's syndrome outcome measures correlate with health status in primary Sjögren's syndrome? *Rheumatology* 2015; 54: 655-9.
15. ALUNNO A, BARTOLONI E, VALENTINI V *et al*.: Discrepancy between subjective symptoms, objective measures and disease activity indexes: the lesson of primary Sjögren's syndrome. *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S210-4.
16. SEROR R, GOTTENBERG JE, DEVAUCHELLE-PENSEC V *et al*.: European League Against Rheumatism Sjögren's Syndrome Disease Activity Index and European League Against Rheumatism Sjögren's Syndrome Patient-Reported Index: a complete picture of primary Sjögren's syndrome patients. *Arthritis Care Res* 2013; 65: 1358-64.
17. INANC N, SAHINKAYA Y, MUMCU G *et al*.: Evaluation of salivary gland ultrasonography in primary Sjögren's syndrome: does it reflect clinical activity and outcome of the disease? *Clin Exp Rheumatol* 2019; 37 (Suppl. 118): S140-5.
18. PARK EH, HA YJ, KANG EH, SONG YW, SCOFIELD RH, LEE YJ: Baseline disease activity influences subsequent achievement of patient acceptable symptom state in Sjögren's syndrome. *Rheumatology* 2020 Nov 14.
19. SHIBOSKI CH, SHIBOSKI SC, SEROR R *et al*.: 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. *Arthritis Rheumatol* 2017; 69: 35-45.
20. VILLA A, WOLFF A, NARAYANA N *et al*.: World Workshop on Oral Medicine VI: A systematic review of medication-induced salivary gland dysfunction. *Oral Dis* 2015; 5: 365-82.
21. CHARLSON M, POMPEI P, ALEX K *et al*.: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 45: 373-83.
22. NAVAZESH M: Methods of collecting saliva. *Ann NY Acad Sci* 1993; 694: 72-7.
23. SEROR R, BOOTSMA H, SARAUX A *et al*.: Defining disease activity states and clinically meaningful improvement in primary Sjögren's syndrome with EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI). *Ann Rheum Dis* 2016; 75: 382-9.
24. PERTOVAARA M, KORPELA M: ESSPRI and other patient-reported indices in patients with primary Sjögren's syndrome during 100 consecutive outpatient visits at one rheumatological clinic. *Rheumatology* 2014; 53: 927-31.
25. BEZZINA O, GALLAGHER P, MITCHELL S *et al*.: Subjective and objective measures of dryness symptoms in primary Sjögren's syndrome: capturing the discrepancy. *Arthritis Care Res* 2017; 69: 1714-23.
26. HIJJAW O, ALAWNEH M, OJJOH K *et al*.: Correlation between Xerostomia index, Clinical Oral Dryness Scale, and ESSPRI with different hyposalivation tests. *Open Access Rheumatol* 2019; 11: 11-8.
27. FERNÁNDEZ-MARTÍNEZ G, ZAMORA-LE-

GOFF V, HERNÁNDEZ MOLINA G: Oral health-related quality of life in primary Sjögren's syndrome. *Reumatol Clin* 2020; 16: 92-6.
28. LACKNER A, BOSCH P, ZENZ S *et al*.: Go ask your patients! PSS-QoL reported perception of dryness correlates with lacrimal and salivary flow in primary Sjögren's syndrome. *Front Med* 2021; 8: 660580.
29. LI Z, FU T, LI L *et al*.: Prevalence, severity, and predictors of dry eye and dry mouth in Chinese patients with primary Sjögren syndrome. *Clin Rheumatol* 2018; 37: 2971-9.
30. ALBRECHT K, DÖRNER T, REDEKER I *et al*.: Comorbidity and health care utilisation in persons with Sjögren's syndrome: a claims data analysis. *Clin Exp Rheumatol* 2020; 38 (Suppl. 126): S78-84.
31. PEGO-REIGOSA JM, RESTREPO J, BALDINI C, RÚA-FIGUEROA FERNÁNDEZ DE LARRINOA Í: Comorbidities (excluding lymphoma) in Sjögren's syndrome. *Rheumatology* 2021; 60: 2075-84.
32. TORRENTE-SEGARRA V, COROMINAS H, SÁNCHEZ-PIEDRA C *et al*.: Fibromyalgia prevalence and associated factors in primary Sjögren's syndrome patients in a large cohort from the Spanish Society of Rheumatology registry (SJOGRENSER). *Clin Exp Rheumatol* 2017; 35 (Suppl. 105): S28-34.
33. CUI Y, LI L, YIN R *et al*.: Depression in primary Sjögren's syndrome: a systematic review and meta-analysis. *Psychol Health Med* 2018; 23: 198-209.
34. GONZALES JA, CHOU A, ROSE-NUSSBAUMER JR *et al*.: How are ocular signs and symptoms of dry eye associated with depression in women with and without Sjögren syndrome? *Am J Ophthalmol* 2018; 191: 42-8.
35. CUI Y, XIA L, LI L, ZHAO Q, CHEN S, GU Z: Anxiety and depression in primary Sjögren's syndrome: a cross-sectional study. *BMC Psychiatry* 2018; 18: 131.
36. DURET PM, MEYER N, SARAUX A *et al*.: Seasonal effect on fatigue, pain and dryness in primary Sjögren's syndrome. *Arthritis Res Ther* 2020; 22: 39.
37. MEINERS PM, ARENDS S, BROUWER E *et al*.: Responsiveness of disease activity indices ESSPRI and ESSDAI in patients with primary Sjögren's syndrome treated with rituximab. *Ann Rheum Dis* 2012; 71: 1297-302.
38. MEINERS P, VISSINK A, KROESE F *et al*.: Abatacept treatment reduces disease activity in early primary Sjögren's syndrome (open-label proof of concept ASAP study). *Ann Rheum Dis* 2014; 73: 1393-6.
39. MARIETTE X, SEROR R, QUARTUCCIO *et al*.: Efficacy and safety of belimumab in primary Sjögren's syndrome: results of the BELISS open-label phase II study. *Ann Rheum Dis* 2015; 74: 526-31.
40. CHOI H, KIM NA, LEE JM *et al*.: Risk factors influencing the occurrence and severity of symptomatic dry eye syndrome: a cross-sectional study. *Ophthalmic Epidemiol* 2021; 31: 1-7.