Patient Acceptable Symptom State (PASS) in patients with primary Sjögren's syndrome in daily clinical practice

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Abstract

Objective

To explore Patient Acceptable Symptom State (PASS) in a standard of care cohort of patients with primary Sjögren's syndrome (pSS) and to compare patient characteristics including EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) between PASS and non-PASS groups.

Methods

All pSS patients fulfilling ACR/EULAR classification criteria from the Registry of Sjögren's Syndrome LongiTudinal (RESULT) cohort, who had available PASS data at baseline were included. Patient-reported outcomes included the PASS question: "Considering all the different ways your disease is affecting you, if you were to stay in this state for the next few months, do you consider your current state satisfactory?"; yes: PASS / no: non-PASS.

Results

Of the 278 included pSS patients, 199 (72%) had an acceptable symptom state according to the PASS question, and median ESSPRI was 6 (IQR 4-7). In the PASS group, 118 (59%) patients had an unacceptable symptom state according to ESSPRI (score ≥5). In multivariable regression analyses, ESSPRI and disease duration were independently associated with presence of PASS. The accuracy of ESSPRI to predict PASS was fair (AUC of 0.78). The cut-off point of ESSPRI for presence of PASS with the highest Youden's index was 7.2 (sensitivity 85%, specificity 56%), followed by 5.2 (sensitivity 48%, specificity 90%).

Conclusion

The majority of pSS patients reported being in an acceptable symptom state according to the PASS question, despite high ESSPRI scores. In our standard of care cohort, the optimal cut-off point of ESSPRI to predict PASS is different when focusing on sensitivity (±7) or specificity (±5).

Key words

primary Sjögren's syndrome, patient-reported outcome measures (PROMs), cohort study

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Introduction

Primary Sjögren's syndrome (pSS) is a chronic auto-immune disease which has great impact on patients' lives. Characteristic for the disease is lymphocytic infiltration of salivary and tear glands, leading to dryness symptoms of mouth and eyes. Because pSS can manifest in any organ, the disease has a broad clinical picture with varying symptoms, such as fatigue, neuropathy, arthritis and interstitial lung disease (1). Not only the physical aspects of patients' lives are affected by this disease, pSS also has a large effect on mental, social and financial aspects (2-4). Sicca symptoms, fatigue and pain caused by pSS are associated with a reduced health-related quality of life (hr-QoL) (5). Furthermore, there are limited treatment options available, which mainly consists of local, symptomatic treatment (6).

The limited treatment options in combination with the impact of pSS on hr-QoL may have significant consequences on whether patients find their symptom state acceptable. The patient acceptable symptom state (PASS) has been defined as the value beyond which patients consider themselves well (7), and has been studied in several rheumatic diseases, such as rheumatoid arthritis (RA), axial spondyloarthritis (axSpA) and systemic lupus erythematosus (SLE) (8-10). However, in pSS there are less data available about the PASS. Previously, the European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index (ESSPRI) was developed for pSS to measure three of the most important Sjögren-related symptoms: dryness, fatigue and pain (11). For this score, a cut-off for an acceptable symptom state was defined as a score<5 (12). One of the reasons for development of this cut-off point was to include patients with an ESSPRI unacceptable symptom state (score≥5) in clinical trials (12). This cut-off point is now increasingly used as inclusion criterion in clinical trials. Furthermore, patient-reported outcome measurements (PROMs) are getting more interest from the side of patients, health care workers and from regulatory authorities.

Because pSS has significant consequences for patients' lives, the objective of this study was to explore the PASS in a standard of care cohort of pSS patients and to compare patient characteristics and disease activity, including ESSPRI, between PASS and non-PASS groups.

Methods

Study design and patients

For this cross-sectional study, data from the baseline visit of patients with pSS from the Registry of Sjögren Syndrome LongiTudinal (RESULT) cohort were analysed. The RESULT cohort is an ongoing prospective observational study, which includes patients with incomplete or confirmed pSS at the outpatient clinic of the department of Rheumatology and Clinical Immunology of the University Medical Centre Groningen (UMCG) (13). Inclusion of the RESULT cohort started in January 2016. This study was approved by the Medical Ethics Committee of the UMCG (METc 2014/491) and was conducted according to the declaration of Helsinki. All patients provided written informed consent. Inclusion criteria for the present study were fulfilment of the 2016 American College of Rheumatology (ACR)/EULAR classification criteria for pSS (14), a completed baseline visit before August 2021 and available PASS data at baseline. There were no specific exclusion criteria for this study.

Outcome measurements

All outcome measurements were collected at the baseline visit of the RESULT cohort. Patient-reported outcome measurements (PROMs) were reported through questionnaires, which included the PASS question: "Considering all the different ways your Sjögren's syndrome is affecting you, if you were to stay in this state for the next few months, do you consider your current state satisfactory?"; yes/no. If patients responded 'yes' to this question, we refer to this as the PASS group, if patients responded 'no' to this question, we refer to this as the non-PASS group. Furthermore, the ESSPRI was collected: "How severe has your dryness, fatigue and pain been during the last two weeks?"; scale 0-10

(11). An acceptable ESSPRI symptom state has been defined as a score<5 (12). Patient global disease activity (GDA) and numeric rating scale (NRS) scores for oral, ocular and vaginal dryness were also collected. As measure of fatigue, the Multidimensional Fatigue Index (MFI) was used. For health status and hr-QoL the EuroQoL-5 dimensions (EQ-5D-5L) and Short Form 36 (SF-36) were collected. Systemic disease activity was assessed with the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) (15) and physician GDA. Damage was assessed with the Sjögren's Syndrome Disease Damage Index (SSDDI) (16). Number of tender points was also collected. Furthermore, the unstimulated and stimulated whole salivary flow rates (UWSF and SWSF, respectively), Schirmer's test and Ocular Staining Score (OSS) were collected as objective dryness measurements. Additionally, a salivary gland ultrasonography (SGUS) was performed and assessed with the total Hocevar score. The following laboratory parameters were also collected: total immunoglobulin G (IgG) serum levels, rheumatoid factor (RF), complement C3 and C4, lymphocyte count, anti-SSB positivity and presence of cryoglobulins. Furthermore, demographic data were collected including disease duration, which was calculated as time since pSS diagnosis.

Statistical analysis

Statistical analyses were performed using SPSS version 23.0. For descriptive statistics, mean±SD, median (IQR) and n (%) were used for normally distributed, non-normally distributed and categorical data, respectively. Independent samples t-test, Mann-Whitney U-test or Chi Square test were used to analyse differences between PASS and non-PASS groups. *p*-values of <0.05 were considered statistically significant. Univariable logistic regression was performed with PASS (yes/no) as dependent variable to evaluate which variables were associated with PASS. The explained variance of these variables for PASS was expressed using the Nagelkerke R^2. Furthermore, multivariable logistic regression using the enter method was performed to cor-

Table I. Patient characteristics of all 278 included pSS patients and split for the PASS (n=199) and non-PASS group (n=79).

	Total (n=278)	PASS (n=199)	Non-PASS (n=79)	*p*-value
Gender (female)	248 (89)	177 (89)	71 (90)	0.82
Age (years)	54 (44-64)	57 (44-65)	49 (41-60)	**0.011**
Disease duration (years)	5 (2-11)	6 (2-12)	5 (2-8)	**0.038**
Symptom duration (years)***	12 (6-20)	12 (6-20)	12 (6-18)	0.76
History of MALT lymphoma	40 (14)	33 (17)	7 (9)	0.10
Current immunosuppressive use (any)*	68 (25)	52 (26)	16 (20)	0.29
Hydroxychloroquine*	47 (17)	35 (18)	12 (15)	0.62
Corticosteroid	15 (5)	12 (6)	3 (4)	0.57
Rituximab (past 6 months)	15 (5)	13 (7)	2 (3)	0.25
Other	11 (4)	9 (5)	2 (3)	0.73
Presence of anti-SSA*	238 (86)	172 (87)	66 (84)	0.47
Focus score ≥1[1]	185 (89)	123 (87)	62 (91)	0.40
Patient-reported outcome measurements				
ESSPRI total score	6 (4-7)	5 (4-7)	7 (6-8)	**<0.001**
Dryness	7 (5-8)	6 (4-8)	7 (6-8)	**<0.001**
Fatigue	7 (5-8)	6 (3-7)	8 (7-9)	**<0.001**
Pain	5 (3-7)	5 (2-7)	7 (5-8)	**<0.001**
ESSPRI <5	87 (31)	81 (41)	6 (8)	**<0.001**
Patient GDA	6 (4-8)	5 (3-7)	8 (7-9)	**<0.001**
NRS ocular dryness	7 (4-8)	6 (4-8)	7 (5-8)	**0.010**
NRS oral dryness	7 (5-8)	6 (4-8)	7 (6-8)	**0.005**
NRS vaginal dryness	5 (2-7)	4 (2-6)	5 (3-7)	**0.048**
MFI physical fatigue*	13 (10-17)	12 (8-15)	17 (14-19)	**<0.001**
MFI mental fatigue*	11 (6-13)	10 (5-13)	12 (10-16)	**<0.001**
EQ-5D-5L index score	0.75 (0.63-0.85)	0.80 (0.72-0.86)	0.60 (0.38-0.72)	**<0.001**
SF-36 domains				
Physical functioning	70 (50-90)	80 (60-90)	50 (40-75)	**<0.001**
Social functioning	63 (50-88)	75 (63-100)	50 (25-63)	**<0.001**
Role limitations (physical)	50 (25-69)	50 (38-75)	25 (13-44)	**<0.001**
Role limitations (emotional)	75 (50-100)	92 (58-100)	58 (42-75)	**<0.001**
Mental health	75 (60-85)	80 (65-90)	65 (50-75)	**<0.001**
Vitality	50 (31-63)	56 (38-69)	31 (25-44)	**<0.001**
Pain	67 (45-78)	67 (57-90)	45 (33-67)	**<0.001**
General health	40 (25-55)	40 (30-60)	30 (20-40)	**<0.001**
Clinical outcome measurements				
ESSDAI total score*	4 (2-7)	4 (2-6)	5 (2-9)	0.07
ESSDAI domains*				
Cutaneous	20 (7)	13 (7)	7 (9)	0.49
Respiratory	4 (1)	3 (2)	1 (1)	1.00
Renal	0	0	0	-
Articular	39 (14)	20 (10)	19 (24)	**0.002**
Muscular	1 (0.4)	0	1 (1)	0.28
PNS	12 (4)	7 (4)	5 (6)	0.30
CNS	0	0	0	-
Haematological	112 (41)	85 (43)	27 (35)	0.18
Glandular	68 (25)	44 (22)	24 (31)	0.14
Constitutional	56 (20)	31 (16)	25 (32)	**0.002**
Lymphadenopathy	17 (6)	13 (7)	4 (5)	0.79
Biological	201 (73)	144 (73)	57 (73)	0.95
ESSDAI <5*	167 (61)	128 (65)	39 (50)	**0.019**
Physician GDA***	2 (1-3)	2 (1-3)	2 (2-4)	**0.010**
SSDDI (total score)	2 (1-3)	2 (1-3)	1 (1-2)	**0.012**
Neurological damage	25 (9)	15 (8)	10 (13)	0.18
Pleuropulmonary damage	18 (6)	16 (8)	2 (3)	0.11
Renal impairment	5 (2)	4 (2)	1 (1)	1.00
Lymphoproliferative disease	40 (14)	33 (17)	7 (9)	0.10
Number of tender points (0-18)**	0 (0-6)	0 (0-4)	4 (0-14)	**0.001**
Objective dryness measurements				
Schirmer's test (mm)**.†	3.5 (0.5-9.5)	3.5 (0.5-9.5)	4.3 (1.0-9.9)	0.40
OSS (total score)*.†	2 (0.5-4)	2 (0.5-4)	2 (0-4)	0.19
UWSF (ml/min)*	0.05 (0.01-0.15)	0.04 (0.01-0.14)	0.07 (0.01-0.19)	0.36
SWSF (ml/min)**	0.54 (0.16-0.96)	0.54 (0.15-0.97)	0.57 (0.20-0.96)	0.92
SGUS (total Hocevar score)*	23 (14-29)	24 (15-30)	21 (12-28)	0.14
Laboratory measurements				
IgG (g/L)*	14.3 (10.9-19.1)	14.3 (11.2-19.1)	14.2 (10.4-19.2)	0.90
RF (IU/ml)*	11.5 (2.3-42.8)	11.0 (2.5-39.0)	14.0 (2.0-46.0)	0.77
C3 (g/L)*	1.1 (0.9-1.3)	1.1 (0.9-1.3)	1.1 (1.0-1.3)	0.20
C4 (g/L)*	0.19 ± 0.09	0.20 ± 0.1	0.19 ± 0.06	0.29
Lymphocyte count (10^9/L)*	1.46 ± 0.57	1.40 ± 0.51	1.61 ± 0.68	**0.016**
Presence of anti-SSB*	150 (55)	114 (58)	36 (46)	0.052
Presence of cryoglobulins*	73 (27)	57 (30)	16 (20)	0.10

Data presented as mean ± SD, median (IQR) or n (%). Missing data: *<5% **5-10% ***10-20%. [1]Data available for 67% of patients. †Mean of both eyes. Bold text indicates significant *p*-value.
pSS: primary Sjögren's syndrome; PASS: Patient Acceptable Symptom State; MALT: mucosa-associated lymphoma; ESSPRI: European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index; GDA: global disease activity; NRS: numeric rating scale; MFI: Multidimensional Fatigue Index; EQ-5D: EuroQoL 5 dimensions; SF-36: Short Form 36; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; SSDDI: Sjögren's Syndrome Disease Damage Index; OSS: Ocular Staining Score; UWSF: unstimulated whole salivary flow rate; SWSF: stimulated whole salivary flow rate; SGUS: salivary gland ultrasonography; IgG: immunoglobulin G; RF: rheumatoid factor.

rect for potential confounders gender, age, disease duration and use of any immunosuppressive on the outcome measurements. To evaluate which variables were independently associated with PASS, variables with *p*-values of <0.05 in univariable logistic regression were entered into a forward conditional multivariable logistic regression model. Selection of variables for multivariable modelling was also based on the check of multicollinearity and clinical relevance. Receiver operating curve (ROC) analysis was performed to explore the accuracy of ESSPRI to predict presence of PASS. Area under the curve (AUC) was interpreted as no discrimination (0–0.5), poor accuracy (0.5–0.7), fair (0.7–0.8), good (0.8–0.9) or excellent (0.9–1.0) (17). The optimal cut-off point for ESSPRI was determined according to the highest Youden's index (sum of sensitivity and specificity subtracted by 1). In addition, an anchoring method was performed to determine the 75th centile of the distribution of ESSPRI in the PASS group.

Results

Patient characteristics

From January 2016 until August 2021, 322 incomplete or confirmed pSS patients had a baseline visit in the RESULT cohort. Of these, 278 patients fulfilled the ACR/EULAR classification criteria and had a completed baseline visit with available PASS data. Of the included 278 pSS patients, 248 (89%) were female, median age was 54 years (IQR 44–64), median disease duration was 5 years (IQR 2–11) and median ESSPRI total score was 6 (IQR 4-7) (Table I). In total, 199 (72%) patients reported being in an acceptable symptom state according to the PASS question.

Differences between PASS and non-PASS groups

pSS patients in the PASS group were significantly older (median 57 *vs*. 49 years), and had a longer disease duration (median 6 *vs*. 5 years) than the non-PASS group. No differences were observed in the use of immunosuppressive drugs. ESSPRI total score was significantly lower in the PASS group compared to the non-PASS group (median 5 *vs*. 7). All other PROMs were also significantly different between these groups, including patient GDA, NRS scores for oral, ocular and vaginal dryness (for female patients) and measures for fatigue and hr-QoL (Table I). Patients in the PASS group had significantly more often ESSDAI low disease activity (score<5) than patients in the non-PASS group (65% *vs*. 50%). Of the ESSDAI subdomains, significant differences were found in the articular and constitutional domain. Sjögren-related damage measured with the SSDDI total score was significantly higher in patients with PASS (median 2 *vs*. 1). Patients in the PASS group had significantly less tender points present than patients in the non-PASS group (median 0 *vs*. 4). Furthermore, the PASS group had significantly lower lymphocyte counts compared to the non-PASS group (mean 1.4 *vs*. 1.6 10^9/L). No significant differences were seen in other laboratory measurements or objective dryness measurements between PASS and non-PASS groups (Table I).

Univariable logistic regression analyses showed that PROMs had the highest explained variance for PASS (yes/no) based on the Nagelkerke R^2 (Table II). ESSPRI total score was significantly associated with PASS, with an R^2 of 0.28. Of the ESSPRI subscores, fatigue showed the highest explained variance based on the R^2 (fatigue 0.30, pain 0.18, dryness 0.08). Assessment of fatigue with the MFI also showed significant associations for both physical and mental fatigue with PASS. Furthermore, ESSDAI low disease activity (score <5), physician GDA, SSDDI total score, number of tender points and lymphocyte count were significantly associated with PASS. Both age and disease duration were also associated with PASS in the univariable analyses (Table II). SSDDI total score was no longer significantly associated with PASS after correcting for age, disease duration or use of any immunosuppressive (model with age: OR 1.105, 95% CI 0.969–1.260; with disease duration: OR 1.106, 95% CI 0.969–1.263; with any immunosuppressive use: OR 1.136, 95% CI 0.998–1.294).

For multivariable logistic regression analyses, ESSPRI total score, disease duration, ESSDAI low disease activity, physician GDA, SSDDI total score, number of tender points and lymphocyte count were tested (Table II). Of these, ESSPRI (OR 0.53, 95% CI 0.42–0.66) and disease duration (OR 1.08, 95% CI 1.02–1.14) were identified as independent predictors for PASS. The R^2 improved from 0.26 with only ESSPRI, to 0.31 after disease duration was added in the model.

ESSPRI cut-off point for acceptable symptom state

Of all 278 pSS patients, only 87 (31%) had an acceptable symptom state according to the predefined ESSPRI cut-off point of score <5. The accuracy of ESSPRI to predict PASS was fair, with an AUC of 0.781 (95% CI 0.721–0.840) (Fig. 1). The optimal cut-off point of ESSPRI for presence of PASS was 7.2 based on the highest Youden's index (sensitivity 85% and specificity 56%), followed by a cut-off point of 5.2 (sensitivity 48% and specificity 90%) (Table III). With the anchoring method, the 75th centile of the distribution of ESSPRI in the PASS group was 6.7.

As additional analysis, patient characteristics and outcome measurements were compared between patients of the PASS group with ESSPRI<5 (n=81) and ESSPRI≥5 (n=118). The PROMs were all significantly higher in the patients with ESSPRI≥5. For most other outcome measurements there were no significant differences, except for the number of tender points (median 2 *vs*. 0) and lymphocyte count (median 1.47 *vs*. 1.30), which were both higher in patients with ESSPRI≥5. ESSDAI total score was somewhat higher in patients with ESSPRI≥5, although not statistically significant (median 4 *vs*. 3, *p*=0.08).

Discussion

In this cross-sectional analysis of pSS patients included in our prospective, observational RESULT cohort, 72% reported being in an acceptable symptom state according to the PASS question. In contrast, only 31% of patients reported an acceptable ESSPRI symptom

Table II. Logistic regression with PASS (yes/no) as dependent variable with demographic, patient-reported, clinical and serological parameters of interest.

	Univariable analysis			Multivariable analysis	
	OR (95% CI)	Nagelkerke R^2	*p*-value	OR (95% CI)	*p*-value
Gender	0.907 (0.386-2.131)	0.000	0.82		a
Age	1.024 (1.005-1.044)	0.031	**0.015**		b
Disease duration	1.066 (1.021-1.113)	0.052	**0.004**	1.080 (1.024-1.139)	**0.005**
History of MALT lymphoma	2.045 (0.864-4.838)	0.015	0.10		a
Current immunosuppressive use (any)*	1.402 (0.744-2.642)	0.006	0.30		a
Presence of anti-SSA*	1.303 (0.632-2.687)	0.003	0.47		a
Patient-reported outcome measurements					
ESSPRI (total)	0.512 (0.416-0.632)	0.276	**<0.001**	0.525 (0.418-0.660)	**<0.001**
Dryness	0.769 (0.668-0.885)	0.077	**<0.001**		c
Fatigue	0.551 (0.457-0.664)	0.298	**<0.001**		c
Pain	0.713 (0.631-0.806)	0.180	**<0.001**		c
Patient GDA	0.523 (0.433-0.631)	0.341	**<0.001**		c
NRS ocular dryness	0.840 (0.744-0.948)	0.044	**0.005**		c
NRS oral dryness	0.824 (0.731-0.928)	0.057	**0.001**		c
NRS vaginal dryness	0.909 (0.824-1.002)	0.022	0.054		a
MFI physical fatigue*	0.713 (0.649-0.783)	0.354	**<0.001**		c
MFI mental fatigue*	0.871 (0.819-0.926)	0.106	**<0.001**		c
Clinical outcome measurements					
ESSDAI (total score)*	0.958 (0.908-1.010)	0.013	0.11		a
ESSDAI <5*	1.882 (1.105-3.206)	0.028	**0.020**		d
Physician GDA***	0.783 (0.634-0.967)	0.031	**0.023**		d
SSDDI total score	1.140 (1.002-1.297)	0.022	**0.047**		d
Neurological damage	0.563 (0.241-1.312)	0.009	0.18		a
Pleuropulmonary damage	3.366 (0.756-14.994)	0.017	0.11		a
Renal impairment	1.600 (0.176-14.451)	0.001	0.68		a
Lymphoproliferative disease	2.045 (0.864-4.838)	0.015	0.10		a
Number of tender points**	0.919 (0.880-0.960)	0.079	**<0.001**		d
Objective dryness measurements					
Schirmer's test (mm)**,†	0.977 (0.945-1.009)	0.011	0.15		a
OSS (total score)*,†	1.071 (0.959-1.197)	0.008	0.22		a
UWSF (ml/min)**	1.193 (0.176-8.093)	0.000	0.86		a
SWSF (ml/min)**	1.129 (0.789-1.614)	0.003	0.51		a
SGUS (total Hocevar score)*	1.020 (0.993-1.048)	0.011	0.15		a
Laboratory measurements					
IgG*	1.003 (0.968-1.038)	0.000	0.88		a
RF*	1.000 (0.994-1.006)	0.000	0.99		a
Lymphocyte count*	0.537 (0.340-0.847)	0.037	**0.008**		d
Presence of anti-SSB*	1.681 (0.993-2.846)	0.020	0.053		a

Missing data: * <5%, **5–10%, ***10–20%. † Mean of both eyes. Bold text indicates significant *p*-value. *Abbreviations:* see Table I.
a: The variable was not tested in multivariable regression analysis because of a p-value of ≥0.05 in univariable regression analysis.
b: Age was not tested in multivariable regression analysis because disease duration was included.
c: Patient GDA, ESSPRI subscores, NRS scores and MFI mental and physical fatigue were not tested in multivariable regression analysis because ESSPRI total score was included.
d: ESSDAI LDA, Physician GDA, SSDDI total score, number of tender points and lymphocyte count were not selected during multivariable regression analysis ($p \geq 0.05$).

state of score <5. We found that PASS was independently associated with disease duration and ESSPRI. The accuracy of ESSPRI to predict PASS was fair (AUC of 0.78), which indicates that also other factors play a role for achieving PASS in pSS.

In the study of Seror *et al*. (12), the ESSPRI cut-off point for acceptable symptom state was developed based on the following PASS question: 'Thinking about all the ways your symptoms related to your Sjögren's syndrome (your dryness, your fatigue, your pain and your mental fatigue) are affecting you, do you consider that your current health status is satisfactory?', yes/no. The PASS question that we used is more global since this question did not specifically include the Sjögren-related symptoms which are included in the ESSPRI. This global PASS question has also been used in other rheumatic diseases (8, 9). Although we found that the ESSPRI was the most important determining factor for presence of PASS, we found a different optimal ESSPRI cut-off point for PASS, which may partly be explained by these differences in formulation. In the study of Seror *et al*.

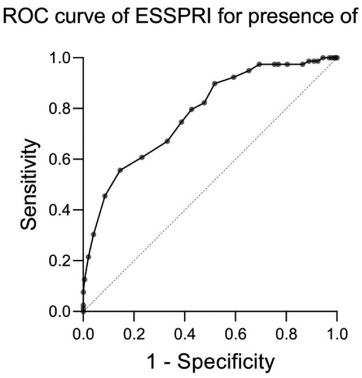

Fig. 1. ROC curve of ESSPRI total score for presence of PASS in pSS patients with an AUC of 0.781 (95% CI 0.721-0.840).

Table III. Sensitivity and specificity of several cut-off points of ESSPRI total score for presence of PASS.

	Sensitivity	Specificity
ESSPRI <5	40.7%	92.4%
ESSPRI <5.2	48.2%	89.9%
ESSPRI <6	57.3%	79.7%
ESSPRI <7	76.9%	60.8%
ESSPRI <7.2	85.4%	55.7%

(12), two possible cut-off points, 5 or 6, were selected based on ROC analysis and the anchoring method from two cohorts. The lower cut-off point was selected because this cut-off point classified more patients in the PASS/non-PASS groups and because this cut-off point would enable inclusion of more patients with an unacceptable symptom state in clinical trials. In our study, the optimal cut-off point based on the highest combined sensitivity and specificity was approximately 7, which shows a higher sensitivity for acceptable symptom state according to the PASS question (85%) but low specificity (56%). A cut-off point of <5 shows a lower sensitivity (41%), but higher specificity (92%), which would lead to selection of more patients with an unacceptable symptom state, also in our standard of care cohort. A previous longitudinal study by Park *et al*. (18) evaluated the presence of acceptable symptom state based on the ESSPRI in a cohort of 102 pSS patients. In this study, 46% of patients reported an acceptable symptom state (ESSPRI<5) at baseline, which was higher than the percentage in our study (31%). This may be due to the fact that our cohort is in a tertiary referral centre, which may lead to inclusion of patients with more complex disease. This is also reflected by the ESSDAI scores in our cohort, which were ≥5 in 39% of our included patients, compared to 16% in the study by Park *et al*. (18). In the study by Seror *et al*. (12), 38% of patients were in an acceptable symptom state according to ESSPRI in the ASSESS cohort, and this was 32% in the EULAR cohort, which was more comparable to the findings in our study. Another observational cohort study, showed that 38% had an ESSPRI score <5, which was also comparable to our cohort (19).

We found that PASS was independently associated with ESSPRI and disease duration, although the explained variance of these parameters to predict PASS was low (Nagelkerke R^2 0.31). This indicates that there might be other factors which play a role in achieving PASS, such as disease perception and coping, which we did not evaluate in this study. It is notable that although ESSPRI scores were high, the majority of pSS patients reported being in an acceptable symptom state according to the PASS question. A possible explanation might be that patients adjust to their symptoms, and are therefore more likely to evaluate their health state as acceptable. It is known that a response shift can occur in patients with chronic diseases, which means that a change occurs in a patient's self-evaluation of their health state (20). This explanation is supported by our finding that patients with PASS had a longer disease duration. This association of PASS with disease duration was also seen in previous studies in RA and axSpA (8, 21), although not all studies in axSpA observed an association with disease duration (10). Our finding that damage according to the SSDDI was more pronounced in the PASS group, may also be explained by the longer disease duration in this group, since the significant association disappeared after correcting for disease duration as potential confounder in a multivariable model.

The association of ESSPRI with PASS was most pronounced for the ESSPRI fatigue subscore, more than for the pain and dryness subscores. Physical and mental fatigue measured with the MFI were also significantly associated with PASS. In accordance with our findings, previous studies have shown that fatigue is also very important for hr-QoL of pSS patients (5, 22). Previous data from our rituximab trial showed that physical fatigue characterises patient experiences of pSS. At baseline, 86% of pSS patients rated physical fatigue as the complaint most eligible for improvement, followed by symptoms of pain and dryness (23). In the present study, we also found associations of ESSDAI low disease activity, physician GDA, number of tender points and lymphocyte count with PASS, but these measures were not independently associated in the multivariable model with PASS. This is in line with previous studies which found that PROMs regarding Sjögren-related symptoms, such as the ESSPRI, are most important for QoL, whereas ESSDAI is of less relevance (5). Furthermore, we found that PASS was not associated with the objective dryness measurements for the tear and salivary glands. Since previous research showed that subjective and objective dryness measurements also show poor correlations, this is not an unexpected finding (24). However, an observational cohort study in 130 pSS patients found that patients with an ESSPRI≥5 had lower UWSF scores than patients with ESSPRI<5 (19). Since the ESSPRI includes a question specifically about dryness and the PASS is a global question, this might explain this difference.

Limitations of this study include the cross-sectional design, in which it is not possible to explore causality or changes in PASS or ESSPRI during follow-up. Because we found an association with disease duration it may be interesting to assess whether the percentage of patients with PASS increases during follow-up. Furthermore, because the RESULT cohort is in a tertiary referral centre, our study population may include patients with more complex disease than in the general pSS population.

In conclusion, the majority of pSS patients reported being in an acceptable symptom state according to the PASS question, despite high ESSPRI scores in this group. We found a differ-

ent optimal ESSPRI cut-off point for presence of PASS when focusing on a higher sensitivity (approximately 7) or a higher specificity (approximately 5). The previously defined ESSPRI cut-off point for acceptable symptom state (score <5) allows for more inclusion of patients with an unacceptable symptom state than a higher cut-off point, which is preferred for clinical trials.

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