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Original article

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

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Abstract

Objective. To investigate the significant determinants of health-related quality of life (HRQOL) and the association of the EULAR Sjögren's syndrome patient reported index (ESSPRI) with clinical parameters including HRQOL in Korean patients with primary Sjögren's syndrome (pSS) compared with non-SS sicca patients.

Methods. We prospectively analysed 104 pSS and 42 non-SS sicca patients. Clinical data including Short Form 36 (SF-36) scores, self-assessments for symptoms and ESSPRI were cross-sectionally collected.

Results. Although most self-assessments and HRQOL statuses were comparable, different association patterns between HRQOL and symptoms were observed in pSS and non-SS sicca patients. pSS patients with low HRQOL had significantly higher ESSPRI scores [$P = 7.6 \times 10^{-6}$ for physical component summary (PCS) subgroups and $P = 0.0015$ for mental component summary (MCS) subgroups] and ESSPRI scores showed a significant association with all SF-36 scales in pSS patients (all $P \leqslant 0.0020$). Moreover, in multivariate linear regression analyses, ESSPRI ($P = 0.035$) and depression ($P = 4.1 \times 10^{-14}$) were significantly correlated with the PCS and the MCS, respectively. However, in the non-SS sicca group, xerostomia inventory (XI) scores were higher in the low PCS subgroup ($P = 0.031$) and this correlated with five SF-36 scales (all $P \leqslant 0.046$). XI scores ($P = 0.0039$) and anxiety ($P = 7.9 \times 10^{-10}$) were the main determinants of the PCS and MCS, respectively.

Conclusion. HRQOL levels were differentially associated with clinical facets in pSS and non-SS sicca patients, although the groups had similar clinical symptoms and HRQOL reduction. Because depression and ESSPRI are major determinants of HRQOL in Korean pSS patients, ESSPRI is suggested to be disease-specific for pSS.

Key words: primary Sjögren's syndrome, health-related quality of life, EULAR Sjögren's syndrome patient reported index, depression.

CLINICAL SCIENCE

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Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by a progressive lymphocytic infiltration of the exocrine glands leading to dry eyes and mouth. The prevalence of SS is estimated to be approximately 0.5–1.0% of the general population and is considered the second most common rheumatic disease [1, 2]. Although some primary SS (pSS) patients can develop severe extraglandular manifestations (including small vessel vasculitis, lung disease, renal disease, and nervous system involvement) and malignant lymphoma, most patients suffer from benign subjective symptoms such as sicca symptoms, arthralgia and fatigue [3]. Although pSS has a profound impact on health-related quality of life (HRQOL) and functional disability, the overall mortality rate has been reported to be similar to that of the general population [1, 4–7]. In this context, it is undisputed that HRQOL assessment is more important in understanding the disease burden in pSS patients than the traditional hard outcome measures such as mortality. Furthermore, since there is no curative treatment and improvement of HRQOL is a major goal in the treatment in pSS, information on the major determinants of HRQOL is necessary in selecting appropriate management strategies for pSS patients.

The previous studies showed that HRQOL is considerably compromised in pSS patients [4–7]. The factors contributing to poor HRQOL were reported to be fatigue [8], depression [5, 9], anxiety [9], sicca symptoms [10], musculoskeletal pain [5, 6] and chemosensory perception [11]. All studies related to HRQOL in pSS have been performed in non-Asian countries with the exception of McMillan *et al*.'s study [12]. It is believed, however, that HRQOL assessments may differ based on cultural factors [13]. Moreover, most of the studies included healthy subjects or general populations as controls. Interestingly, Rostron *et al*. [14] and Champey *et al*. [15] showed that generic HRQOL was comparable between patients with pSS and non-Sjögren's sicca (non-SS sicca). However, these two studies did not carry on further investigations into which features of the two different groups were responsible for the reduction in HRQOL.

Recently the EULAR Sjögren's syndrome patient reported index (ESSPRI) was developed as a simple index for measuring pSS patient's symptoms. The ESSPRI is calculated by averaging the scales for pain, fatigue and dryness [16]. It has been shown to correlate well with patient global assessment (PGA) and has been validated in a cohort of 230 pSS patients. However, the cohort consisted of pSS patients exclusively from Europe and the USA and did not include Asian patients. The ESSPRI incorporates relatively common symptoms of SS-like sicca patients, such as dry eyes and mouth syndrome (DEMS) or sicca, asthenia and polyalgia syndrome (SAPS) [17, 18]. Thus it is not clear whether the ESSPRI is specific for pSS or can be applied to patients with features similar to those of pSS.

Herein we investigate the significant determinants of generic HRQOL in Korean patients with pSS and non-SS sicca patients by comparing the two groups with similar clinical features. In addition, we studied the association of the ESSPRI with clinical parameters (including HRQOL) in both groups in order to clarify its significance in pSS patients.

Patients and methods

Patients

We enrolled 104 female pSS patients from August 2005 to July 2011. pSS patients were diagnosed according to the criteria of the American–European Consensus Group (AECG) for pSS at the Rheumatology Clinic, Seoul National University Bundang Hospital [19]. During the same period, 42 female patients presenting with dry mouth or dry eyes were classified into a non-SS sicca group. The non-SS sicca group patients did not fulfil the AECG criteria and did not have a well-defined rheumatic disease. The non-SS sicca group was comprised of patients with the following presentation: DEMS (28 patients) [17], dry eye syndrome (5 patients), drug-induced sicca (5 patients), undifferentiated connective tissue disease (2 patients), burning mouth syndrome (1 patient) and primary RP (1 patient). Because Korean normative data for the Short Form 36 (SF-36) health survey was not available at the time of this study, we used the previous Korean SF-36 scale scores that had been reported for urban women ($n = 428$) and married women working full time ($n = 577$) [20, 21]. In order to compare the SF-36 scores with those of our study subjects, overall means and standard deviations of SF-36 scales were calculated by weighting for the number of subjects included in each above-mentioned study. The study was approved by local ethical committees (IRB no. B-0506/021-004) and written informed consent was obtained from all participants.

Methods

During the first clinical visit, patients completed the Korean version of the SF-36 questionnaire (version 2) in order to assess generic HRQOL and completed the xerostomia inventory (XI) in order to evaluate the severity of xerostomia [22]. The SF-36 has eight components: physical functioning (PF), role limitations owing to physical health (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional health (RE) and mental health (MH). These eight components are aggregated in order to produce a physical component summary (PCS) and a mental component summary (MCS) [23]. All SF-36 scale measures were scored using norm-based methods. Higher SF-36 scores are indicative of better health. Moreover, dry mouth, dry eyes, fatigue, arthralgia, myalgia, depression and anxiety were rated using a 10-cm, visual analogue scale (VAS). PGA was also measured using a VAS. For each item, the time reference was within the past 14 days. ESSPRI and dryness scores were calculated as previously reported [16].

Clinical and laboratory data were collected within 2 weeks of enrolment. The whole saliva flow rate was determined using the spitting method. Unstimulated whole saliva was collected in disposable cups for 15 min. Stimulated whole saliva was collected for 5 min after chewing paraffin wax for 10 s. The Schirmer's test and Rose Bengal staining were performed in order to assess lacrimal dysfunction. Oral health status was evaluated using the decayed/missing/filled surface (DMFS) index [24]. The results of 99mTc-pertechnetate salivary gland scintigraphy were available in 87/104 (83.6%) pSS patients and 26/42 (61.9%) non-SS sicca patients. A minor salivary gland biopsy was performed in 51/104 (49%) pSS patients and in 31/42 (73.8%) non-SS sicca patients. In patients with pSS, the EULAR Sjögren's syndrome disease activity index (ESSDAI) and Sjögren's syndrome disease damage index (SSDDI) were presented as previously defined [25, 26].

Statistical analysis

Continuous values are expressed as the mean ± S.E.M. Differences between means were determined using the Student's *t*-test or analysis of variance (ANOVA) followed by Tukey's multiple comparison tests. Categorical variables were compared using the chi-square test or Fisher's exact test where applicable. Bivariate correlations were assessed using Pearson's correlation coefficient. A multivariate linear regression analysis was performed in order to determine the variables independently associated with each scale of the SF-36 by using a stepwise method. Age, symptom duration and variables with $P < 0.10$ in univariate analyses were subjected to all regression models according to a priori assumptions about potential confounders. Statistical analysis was performed using PASW Statistics 18 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered significant.

Results

Clinical and laboratory features of study subjects

The clinical characteristics of the patients are summarized in Table 1. The mean age of the pSS group was significantly lower than that of the non-SS sicca group ($P = 0.004$). Symptom durations were longer for the pSS group than for the non-SS sicca group ($P = 3.0 \times 10^{-5}$). The prevalence of dry eyes or mouth, musculoskeletal pain or self-reported medical problems (including psychiatric disease) was not different between the two groups. However, objective findings of exocrine gland dysfunction and histological evidence of focal lymphocytic sialoadenitis were more prevalent in pSS patients than in non-SS sicca patients. Additionally, more patients in the pSS group had RP ($P = 0.014$) and cutaneous involvement ($P = 0.020$) than non-SS sicca patients. Expectedly, all autoantibodies (including anti-Ro/SSA and anti-La/SSB) were more common in the pSS group than in the non-SS sicca group. The ESSDAI and SSDDI were 3.03 ± 0.31 (range 0–18) and 1.62 ± 0.11 (range 0–7), respectively, in pSS patients.

Despite the significant impairment in exocrine gland function and higher XI scores (42.0 ± 1.2 *vs* 35.6 ± 1.5, $P = 0.002$) in pSS patients, VAS values for each symptom and PGA scores were not significantly different between pSS and non-SS sicca patients. In bivariate correlation analyses, fatigue (all $P \leqslant 4.6 \times 10^{-6}$) and depression (all $P \leqslant 0.019$) VASs were significantly associated with extraglandular symptoms in the pSS group, while depression VAS correlated with only anxiety in the non-SS sicca group ($P = 1.5 \times 10^{-13}$; Table 2). Additionally, PGA was significantly associated with the self-assessment scores of exocrine (all $P \leqslant 0.012$) and extraglandular (all $P \leqslant 0.031$) symptoms, with the exception of arthralgia, in pSS patients. On the other hand, non-SS sicca patients showed that PGA scores were mainly positively related with the scores of glandular symptoms (all $P \leqslant 0.010$). Dryness scores were significantly associated with PGA scores in both pSS ($P = 4.6 \times 10^{-6}$) and non-SS sicca ($P = 0.0012$) groups.

HRQOL and ESSPRI in pSS and non-SS sicca patients

When scores on the SF-36 scales were compared among pSS patients, non-SS sicca patients and controls, the scores for the BP, GH, VT and MH scales were significantly lower in the pSS group than in the control group (Fig. 1). However, scores on the SF-36 scales were not different between pSS and non-SS sicca patients. Additionally, pSS and non-SS sicca patients had similar values for the PCS (46.1 ± 0.8 *vs* 45.7 ± 1.3) and the MCS (43.1 ± 1.2 *vs* 45.2 ± 2.0) measures. Because the mean ages of the two groups were significantly different, we repeated the comparison of the SF-36 scores after age-matched subgroups were created from pSS and non-SS sicca patients at a 3:1 ratio (age 52.2 ± 1.1 years, $n = 93$ for pSS *vs* age 52.2 ± 1.8 years, $n = 31$ for non-SS sicca). In this subgroup analyses there was no significant difference in HRQOL between age-matched subgroups (data not shown).

The ESSPRI was not significantly different between pSS and non-SS sicca patients (4.65 ± 2.3 *vs* 4.54 ± 2.1). Moreover, the ESSPRI positively correlated with PGA in pSS patients (Pearson's correlation coefficient $\rho = 0.44$, $P = 3.6 \times 10^{-4}$) and non-SS sicca patients ($\rho = 0.51$, $P = 0.0017$), as previously reported [16]. Interestingly, the ESSPRI was significantly associated with the following clinical variables in pSS patients: XI scores ($\rho = 0.35$, $P = 0.0064$), myalgia ($\rho = 0.52$, $P = 1.9 \times 10^{-5}$), depression ($\rho = 0.45$, $P = 2.8 \times 10^{-4}$) and anxiety ($\rho = 0.57$, $P = 1.3 \times 10^{-6}$). On the other hand, the ESSPRI in non-SS sicca patients correlated with only the XI score ($\rho = 0.47$, $P = 0.0047$).

All subjects were stratified into high and low score groups, based on the 25th and 75th percentile ranges of the PCS or MCS values. Twenty-six (25.0%) and 22 (21.2%) pSS patients and 9 (21.4%) and 13 (31.0%) non-SS sicca patients were classified into the high and low PCS subgroups, respectively. The high MCS subgroup included 22 (21.2%) pSS and 14 (33.3%) non-SS

Table 1 Demographic and clinical characteristics of the study subjects

	Non-SS sicca group ($n = 42$)	pSS group ($n = 104$)	P-value**
Age, mean (S.E.M.), years	56.2 (1.6)	50.1 (1.2)	0.004
Symptom duration, mean (S.E.M.), years	4.1 (0.7)	8.2 (0.7)	3.0×10^{-5}
Dry eye symptoms, years	83.3	85.6	0.732
Dry mouth symptoms, years	83.3	86.5	0.617
Lacrimal dysfunction	42.9	73.7	5.0×10^{-5}
Schirmer test $\leqslant$ 5 mm/5 min	41.5 (17/41)	66.3 (61/92)	0.007
Rose Bengal stain score $\geqslant$ 4	9.5 (4/42)	39.5 (34/86)	4.0×10^{-4}
Focal lymphocytic sialoadenitis	6.5 (2/31)	74.5 (38/51)	6.0×10^{-10}
Salivary dysfunction	73.8	98.1	2.0×10^{-5}
Unstimulated salivary flow, mean (S.E.M.), ml/min	0.43 (0.18)	0.05 (0.007)	0.039
Abnormal salivary gland scan	69.2 (18/26)	96.6 (84/87)	3.0×10^{-4}
Autoantibodies			
Anti-SSA/Ro	2.4	91.3	3.0×10^{-26}
Anti-SSB/La	4.8	50.0	4.3×10^{-8}
RF	12.5	47.0	1.9×10^{-4}
ANA	23.1	61.6	4.6×10^{-5}
DMFS index, mean (S.E.M.)[a]	12.1 (1.2)	13.3 (0.9)	0.433
Arthralgia/arthritis	40.5	38.5	0.821
Myalgia	33.3	36.0	0.797
RP	4.8	22.1	0.014
Cutaneous involvement	0.0	12.5	0.020
CNS/PNS involvement	0.0	8.7	0.060
Past medical history			
Hypertension	14.3	16.3	0.757
Diabetes	2.4	2.9	1.000
Psychiatric disease	7.1	3.8	0.411
Thyroidal illness	9.5	18.3	0.220
ESSDAI, mean (S.E.M.)[b]	—	3.03 (0.31)	
SSDDI, mean (S.E.M.)[c]	—	1.62 (0.11)	

Values are percentage or percentage (n/n) unless otherwise stated. [a]Decayed, missing, filled surfaces index; [b]EULAR Sjögren's syndrome disease activity index; [c]Sjögren's syndrome disease damage index. **P-value by t-test, chi-square test, or Fisher's exact test.

sicca patients and the low MCS subgroup included 26 (25.0%) pSS and 9 (21.4%) non-SS sicca patients. When patient's assessment scores were compared between the high and low score groups, pSS and non-SS sicca patients showed different patterns of clinical features (Fig. 2).

Among pSS patients, the ESSPRI (5.44 ± 0.30 *vs* 3.24 ± 1.17, $P = 7.6 \times 10^{-6}$) and VASs of fatigue (6.0 ± 0.51 *vs* 3.27 ± 0.40, $P = 1.1 \times 10^{-4}$), arthralgia (4.55 ± 0.69 *vs* 1.0 ± 0.33, $P = 6.2 \times 10^{-5}$) and myalgia (4.27 ± 0.56 *vs* 0.81 ± 0.24, $P = 3.8 \times 10^{-6}$) were significantly higher in the low PCS subgroup than in the high PCS subgroup (Fig. 2A).

In contrast, in non-SS sicca patients, the VAS of dry mouth (8.00 ± 0.65 *vs* 4.83 ± 1.11, $P = 0.019$) and the XI scores (41.30 ± 3.22 *vs* 29.67 ± 3.18, $P = 0.031$) were the only significantly different variables. When compared between the low and high MCS subgroups, depression and anxiety VASs were significantly higher in the low MCS subgroups for both pSS ($P = 3.2 \times 10^{-9}$ and $P = 2.9 \times 10^{-8}$, respectively) and non-SS sicca patients ($P = 8.4 \times 10^{-7}$ and $P = 2.9 \times 10^{-7}$, respectively; Fig. 2B). However, the distributions of the ESSPRI (5.95 ± 0.41 *vs* 3.68 ± 0.49, $P = 0.0015$) and fatigue VAS (6.38 ± 0.52 *vs* 3.80 ± 0.48, $P = 9.2 \times 10^{-4}$) were different between the high and low MSC subgroups only in pSS patients.

Correlation between clinical variables and HRQOL in pSS and non-SS sicca patients

The VASs of fatigue ($\rho = -0.34$ to -0.48, all $P \leqslant 0.0013$) and arthralgia ($\rho = -0.21$ to -0.56, all $P \leqslant 0.032$) correlated significantly with all scales and summary scores of the SF-36 in pSS patients. Surprisingly, the ESSPRI was significantly associated with all SF-36 scales and summary scores in pSS patients ($\rho = -0.41$ to -0.69, all $P \leqslant 0.0020$; Table 3). However, the ESSPRI showed negative correlations with regard to only four of the scale scores in non-SS sicca patients, whereas XI scores correlated with six scores of the SF-36. Because multiple variables were associated, a multivariate linear regression analysis was performed in order to identify the parameters most strongly associated with each SF-36 score. As summarized in Table 4, the depression VAS significantly correlated with all SF-36 scales in pSS patients (with the exception of PF and GH). Furthermore, the ESSPRI in the pSS group was an independent determinant of PF, GH, VT and PCS scores. Fatigue, anxiety, myalgia and

Table 2 Bivariate correlations between self-assessment scores in patients with pSS and non-SS sicca

	Dryness score[a]		Fatigue		Depression		PGA[b]	
	Non-SS sicca	pSS	Non-SS sicca	pSS	Non-SS sicca	pSS	Non-SS sicca	pSS
Dry mouth	0.95 (0.90, 0.97; 2.9×10^{-18})[c]	0.94 (0.91, 0.96; 4.8×10^{-31})					0.49 (0.20, 0.71; 0.0027)	0.34 (0.10, 0.54; 0.0068)
Dry eyes	0.66 (0.42, 0.82; 1.5×10^{-5})	0.58 (0.40, 0.73; 4.1×10^{-7})		0.25 (0.02, 0.46; 0.036)			0.44 (0.14, 0.66; 0.0059)	0.40 (0.18, 0.58; 6.5×10^{-6})
XI score[d]	0.61 (0.35, 0.78; 9.7×10^{-5})	0.77 (0.65, 0.85; 9.9×10^{-14})	0.35 (0.01, 0.61; 0.042)	0.31 (0.08, 0.51; 0.014)			0.43 (0.13, 0.66; 0.010)	0.32 (0.09, 0.52; 0.012)
Dryness score[a]				0.27 (0.02, 0.49; 0.035)			0.53 (0.24, 0.73; 0.0012)	0.42 (0.21, 0.60; 7.3×10^{-6})
Myalgia				0.49 (0.33, 0.63; 2.2×10^{-7})		0.31 (0.12, 0.48; 0.0018)	0.45 (0.16, 0.66; 0.0031)	0.22 (0.02, 0.40; 0.031)
Arthralgia				0.45 (0.28, 0.59; 2.5×10^{-6})		0.23 (0.04, 0.41; 0.019)		
Fatigue		0.27 (0.03, 0.48; 0.035)				0.45 (0.27, 0.59; 3.6×10^{-6})		0.29 (0.10, 0.46; 0.0030)
Depression				0.45 (0.27, 0.59; 3.6×10^{-6})				0.31 (0.12, 0.47; 0.0019)
Anxiety				0.44 (0.27, 0.59; 4.6×10^{-6})	0.87 (0.76, 0.93; 1.5×10^{-13})	0.82 (0.74, 0.87; 1.1×10^{-24})		0.39 (0.21, 0.54; 6.0×10^{-5})
PGA[b]	0.53 (0.24, 0.73; 0.0012)	0.42 (0.20, 0.60; 4.6×10^{-4})		0.29 (0.10, 0.46; 0.0030)		0.31 (0.12, 0.47; 0.0019)		

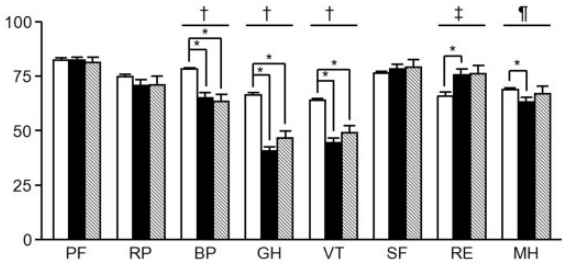
[a]Calculated as previously reported [16]; [b]patient's global assessment; [c]Pearson's correlation coefficient (95% CI; *P*-value); [d]xerostomia inventory.

arthralgia correlated significantly with one or two scales of the SF-36. The ESSDAI and SSDDI were not associated with any scales of the SF-36. On the other hand, in the non-SS sicca group, XI scores and anxiety VASs were major determinants of HRQOL (Table 4).

Discussion

SS is believed to have a significant effect on HRQOL, according to a number of studies conducted in non-Asian populations [4–11]. In our study, we compared the generic HRQOL status of SS female patients with the Korean women previously presented (due to the lack of up-to-date, normative data in Korea). Although circumstantial, Korean SS patients had significantly lower scores on the four SF-36 scales (BP, GH, VT and MH) than controls.

Fig. 1 SF-36 scores obtained in each domain and summary component scales in the study subjects.



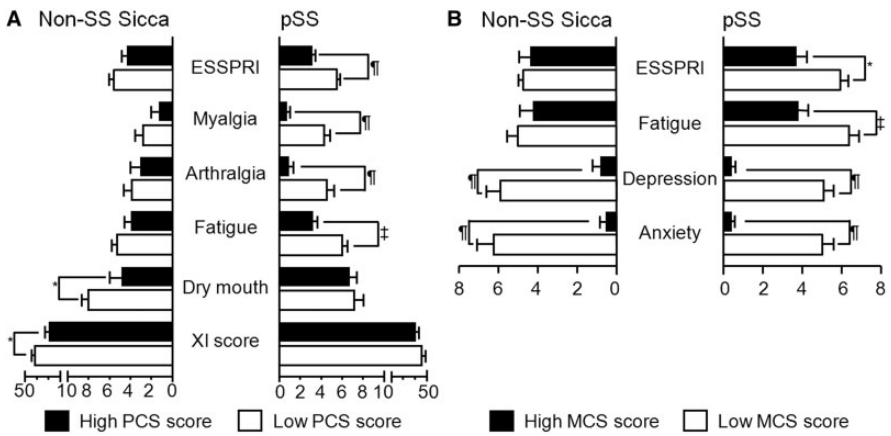
White bars represent SF-36 scores of Korean women combined from the previous reports [20, 21]. Black or hatched bars represent patients with pSS or non-SS sicca, respectively. There was no significant difference in SF-36 scores between the pSS and non-SS sicca patients. Each bar indicates mean ± S.E.M. $^{*}P < 0.05$ by Tukey's multiple comparison tests; $^{\dagger}P < 0.0001$ by ANOVA; $^{\ddagger}P < 0.05$ by ANOVA; $^{\P}P < 0.01$ by ANOVA.

Even allowing for low disease activity (the mean ESSDAI of 3.03), these results are consistent with those of previous research findings in non-Asian populations.

Of note, there were no significant differences in any of the HRQOL scale scores between patients with pSS and non-SS sicca. This was not a surprising finding considering that the two groups had a similar prevalence of symptoms and similar self-assessment scores (including ESSPRI). These results agree with the results of the studies conducted by Rostron *et al*. [14] and Champey *et al*. [15]. In the study of Rostron *et al*., the HRQOL of pSS patients was compared with that of xerostomia patients without extraoral manifestations. On the other hand, Champey *et al*. enrolled sicca patients with asthenia or limb pain but excluded those with autoimmune features (i.e. SAPS). As already pointed out in the study of Champey *et al*. [15], non-SS sicca patients have a similar clinical presentation and level of HRQOL with separate pathogenic mechanisms, as the objective findings of autoantibodies and/or focal lymphocytic infiltration are clearly distinctive of the pSS group.

Although pSS and non-SS sicca patients reported comparable clinical features and HRQOL scores, our study showed that determinants for HRQOL were collectively quite different between the two groups. According to bivariate correlation analyses, XI scores (a severity index of xerostomia) correlated significantly with the physical health scales (PF, RP, BP and PCS) and the GH scale in non-SS sicca patients. In contrast, pSS patients did not show any correlation between XI scores and SF-36 scales. Furthermore, despite a significant correlation between the ESSPRI and XI scores or PGA in both groups, the ESSPRI correlated significantly with the scores of all SF-36 scales in only pSS patients. In addition, when compared between subjects with high *vs* low PCS or MCS scores, the ESSPRI showed a significantly different distribution in only pSS patients. Moreover, multivariate analyses revealed good correlations between the ESSPRI and

Fig. 2 Comparison of clinical variables between patients with high *vs* low scores on the (**A**) PCS or (**B**) MCS.



High or low scores were defined as ⩾75th percentile or ⩽25th percentile value observed among total subjects. $^{*}P < 0.05$; $^{\dagger}P < 0.01$; $^{\ddagger}P < 0.001$; $^{\P}P < 0.0001$ by *t*-test.

Table 3 Bivariate correlations between the ESSPRI or xerostomia inventory scores and SF-36 scale scores

	Non-SS sicca				pSS			
	XI score		ESSPRI		XI score		ESSPRI	
	ρ[a]	*P*-value	ρ	*P*-value	ρ	*P*-value	ρ	*P*-value
PF	−0.34 (−0.60, −0.01)	0.046					−0.42 (−0.61, −0.19)	8.3×10^{-4}
RP	−0.58 (−0.77, −0.31)	2.4×10^{-4}	−0.39 (−0.64, −0.07)	0.020			−0.44 (−0.62, −0.21)	4.3×10^{-4}
BP	−0.44 (−0.67, −0.13)	0.0082	−0.50 (−0.71, −0.20)	0.0023			−0.50 (−0.64, −0.24)	2.0×10^{-4}
GH	−0.44 (−0.67, −0.12)	0.011	−0.40 (−0.65, −0.08)	0.022			−0.61 (−0.75, −0.42)	2.0×10^{-7}
VT							−0.52 (−0.68, −0.31)	1.9×10^{-5}
SF							−0.50 (−0.66, −0.28)	4.9×10^{-5}
RE	−0.35 (−0.61, −0.02)	0.041					−0.39 (−0.58, −0.15)	0.0020
MH							−0.41 (−0.60, −0.17)	0.0012
PCS	−0.49 (−0.71, −0.19)	0.0039	−0.37 (−0.63, −0.04)	0.034			−0.48 (−0.65, −0.25)	1.1×10^{-4}
MCS							−0.48 (−0.65, −0.26)	1.0×10^{-4}

[a]Pearson's correlation coefficient (95% CI).

PF, GH or VT scales. These results confirmed the validity of the ESSPRI in pSS patients and suggested that the ESSPRI could have disease-specific meaning beyond a simple quantitative index of the three common symptoms.

The prevalence of depression is higher and can seriously affect HRQOL in pSS patients [5, 9, 27–29]. In our study there was no difference in VAS levels of depression between the pSS and non-SS sicca groups, and depression was strongly associated with anxiety in both groups. In pSS patients, depression also correlated with a variety of clinical features, including fatigue, arthralgia, myalgia and PGA. Interestingly, although there was no correlation with exocrine symptoms, depression moderately correlated with the ESSPRI ($\rho = 0.45$) in pSS patients. Multivariate analyses clearly showed that depression negatively impacts most aspects of HRQOL in pSS patients. These results suggest that depression is the most important determinant of HRQOL (especially with regards to mental health) in Korean pSS patients and were consistent with those previously reported by Segal *et al*. [5]. It has often been recommended that the use of medications that exacerbate sicca symptoms should be avoided in pSS patients [30], and it is well known that dry mouth is a common side effect of many antidepressants [31]. However, Simmons *et al*. [32] reported that stimulated parotid salivary flow rates were not different between pSS patients taking xerostomic medications and those not taking xerostomic medications. Within respect to these findings, appropriate recognition and treatment for depression may be essential for improving HRQOL in pSS patients. On the other hand, treatments focused on dryness or anxiety may enhance HRQOL in non-SS sicca patients because their PCS and MCS scores were associated with XI scores and anxiety in multivariate analyses.

Fatigue is another common and important symptom and has been reported to be related to a reduction in HRQOL in pSS [8, 33–35]. As expected, in our pSS patients, univariate analysis showed that fatigue moderately correlated with all domains of the SF-36, PGA, depression and anxiety. Moreover, fatigue and depression VASs were significantly higher in patients with low PCS or MCS scores than in those with higher scores. However, fatigue was not a significant determinant of HRQOL in non-SS patients. Segal *et al*. [35] reported that depression was associated with, and partially accounted for, fatigue in pSS patients. In addition, Barendregt *et al*. [36] and Bax *et al*. [37] revealed that depression was the most relevant cause of fatigue in pSS patients. However, an association between fatigue and the RP or RE scales remained statistically significant after multivariate linear regression analyses in our study. Although common biological mechanisms may underlie both depression and fatigue [38], fatigue may independently affect HRQOL in Korean pSS patients. Active therapy for fatigue is necessary in order to improve HRQOL in pSS patients, but no specific treatment for fatigue has been established. There is some evidence indicating that fatigue caused by pSS may be mediated by immune-endocrinological mechanisms [38]. Further, recent immunological therapies including rituximab and anakinra have been shown to improve fatigue in pSS patients [39–41]. However, considering that most pSS patients have a benign course and the cost-effectiveness of immunological therapy for fatigue has not been evaluated, aerobic exercises have remained the preferred treatment option for fatigue [42].

There are several limitations to the present study that need to be addressed. First, we could not compare HRQOL levels between Korean pSS patients and age-matched controls. As mentioned above, we obtained SF-36 scores from previous studies by using subgroups of Korean women, owing to a lack of normative data on the general Korean population. However, our study focused on the significant determinants of HRQOL in patients with pSS and non-SS sicca. Second, the sample size of the non-SS sicca group ($n = 42$) may not have been large enough to study the different determinants of HRQOL in pSS and non-SS sicca patients. Third, our pSS patients had a low level of disease activity, with a mean ESSDAI score of 3.03. The mean ESSDAI score of the original clinical studies on patients with pSS from

Table 4 Standard regression coefficients (β) on multiple linear regression analysis for clinical variables affecting SF-36 scores

	PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS
Non-SS sicca group										
Anxiety				−3.59 (−5.94, −1.23; 0.0041)[a]			−5.80 (−8.41, −3.19; 7.6×10^{-5})	−6.83 (−8.31, −5.35; 7.5×10^{-11})		−3.86 (−4.70, −2.96; 7.9×10^{-10})
XI score	−0.61 (−1.21, −0.12; 0.046)	−1.66 (−2.49, −0.84; 2.4×10^{-4})							−0.42 (−0.70, −0.15; 0.0039)	
Depression					−5.23 (−7.21, −3.24; 6.4×10^{-6})	−5.51 (−8.00, −3.00; 8.5×10^{-5})				
ESSPRI			−6.97 (−11.26, −2.69; 0.0023)							
pSS group										
Depression		−4.15 (−6.76, −0.31; 0.032)	−4.45 (−6.57, −2.33; 9.5×10^{-5})		−3.20 (−5.64, −0.77; 0.011)	−5.63 (−8.74, −2.37; 9.4×10^{-4})	−5.15 (−7.88, −2.42; 3.8×10^{-4})	−3.54 (−6.18, −0.89; 0.010)		−4.17 (−5.01, −3.33; 4.1×10^{-14})
ESSPRI	−3.40 (−5.42, −1.38; 0.0014)			−5.78 (−8.60, −2.95; 1.4×10^{-4})	−4.53 (−7.74, −1.32; 0.0065)				−1.35 (−2.60, −0.10; 0.035)	
Fatigue		−3.53 (−7.07, −1.23; 0.0061)					−2.99 (−5.46, −0.51; 0.019)			
Anxiety						−3.04 (−6.02, −0.07; 0.045)		−4.57 (−7.04, −2.10; 4.9×10^{-4})		
Myalgia				−1.79 (−3.53, −0.04; 0.045)					−0.98 (−1.76, −0.21; 0.013)	
Arthralgia			−3.45 (−5.10, −1.81; 9.5×10^{-5})							

[a]95% CI and *P*-value.

multicentre clinics was 9.04 [25]. Most pSS patients have mild, stable disease [43], and in the study by Risselada *et al*. [44], the mean ESSDAI score from 195 pSS patients was 3.18. Nonetheless, even with the low disease activity in our pSS patients, our results indicate that Korean pSS patients had a poorer HRQOL. Finally, the non-pSS sicca group in the present study was not homogeneous. However, more information on intrinsic determinants of the HRQOL can be extracted from a comparison between pSS patients and patients with SS-like manifestations.

In conclusion, our study showed that HRQOL scores of Korean pSS patients were reduced by the same extent as those of non-SS sicca patients. However, HRQOL levels of the two groups did differ with regards to the following clinical symptoms: depression and the ESSPRI were major determinants of HRQOL in pSS patients, whereas anxiety and XI scores significantly correlated with HRQOL in non-pSS patients. Therefore the ESSPRI may be a disease-specific, self-reporting instrument for monitoring pSS.

Rheumatology key messages

- HRQOL was comparably reduced in pSS and non-SS sicca patients.
- Depression and the ESSPRI were significant determinants of HRQOL in Korean pSS.
- ESSPRI may be disease-specific for pSS.

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