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

J. Lee, J.H. Koh, S.-K. Kwok, S.-H. Park

Division of Rheumatology, Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea.

Abstract Objective

This study was undertaken to evaluate the health-related quality of life (HRQoL) in patients with primary Sjögren's syndrome (pSS) and to identify its predictors among various clinical parameters.

Methods

The EuroQoL-5 dimension (EQ-5D) was used to measure the patients' HRQoL. The utility values of 178 patients with pSS enrolled in a prospective pSS cohort in Korea were analysed and compared with the Korean normative data. The associations among the clinical parameters and utility values were evaluated.

Results

The mean utility value of the pSS patients was significantly lower than that of the Korean general population $(0.773\pm0.138 \text{ vs}. 0.944\pm0.095, p<0.001)$. The proportion of patients with problems in the 4 dimensions was significantly higher in the pSS patients than in the general population (anxiety/depression 70.2 vs. 24.2%, pain 78.7 vs. 28.8%, usual activities 37.6 vs. 9.8%, and mobility 40.4 vs. 12.5%, p<0.001). Bivariate correlation analyses revealed that the degree of pain, fatigue, and patient global assessment of the disease was positively correlated with the utility value. The xerostomia inventory score, ocular surface disease index, and the EULAR Sjögren's syndrome patient-reported index (ESSPRI) also correlated with the utility value. On multiple regression analysis, only the ESSPRI remained in the model after stepwise selection adjusted for age and sex (coefficient $\beta = -0.053$, p<0.001).

Conclusion

The HRQoL of pSS patients is significantly lower than that of the general population, and the ESSPRI is an independent predictor of the HRQoL in pSS patients.

Key words

Sjögren's syndrome, quality of life, patient outcome assessment, ESSPRI, EQ-5D-5L

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Jennifer Lee, MD, PhD Jung Hee Koh, PhD student Seung-Ki Kwok, MD, PhD Sung-Hwan Park, MD, PhD

Please address correspondence to: Sung-Hwan Park, MD, PhD, Division of Rheumatology, Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Banpo-daero 222, Seocho-gu, Seoul 137-701, Republic of Korea. E-mail: rapark@catholic.ac.kr

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Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterised by lymphocytic infiltration of the exocrine glands that results in dry eyes and a dry mouth (1). The prevalence of pSS varies according to the study population or diagnostic criteria used, ranging from 0.03-2.7% (2). Patients with pSS suffer not only from sicca symptoms but may also experience other organ involvements such as arthralgia, Raynaud's phenomenon, cytopenia, interstitial lung disease, and interstitial nephritis. In addition, a substantial number of patients experience severe fatigue (3) and a depressive mood (4). Therefore, it is not surprising that patients with pSS report a low health-related quality of life (HRQoL). In fact, researchers have addressed this issue and reported reduced HRQoL in pSS patients who were evaluated using various measures such as the visual analogue scale (VAS) and short form (SF)-36 questionnaire. According to these studies, the contributing factors to a low HRQoL included fatigue (5-7), depression (8), sicca symptoms (9), and pain (10). After introduction of the EULAR Sjögren's syndrome patient-reported index (ESSPRI), which consists of a numerical rating scale for dryness, pain, and fatigue (11), a high ESSPRI score was added to the list (7, 12, 13). The EuroQoL-5 dimension (EQ-5D) is a generic tool that addresses HROoL provided by EuroQoL. It determines the quality of life of individuals based on 5 domains including mobility, selfcare, usual activities, pain, and anxiety/ depression. Individuals are requested to give score from one (no problem) to three (extreme problem) in EQ-5D-3L or five in EQ-5D-5L for each domain. Then utility values are obtained for each combination of states using social preference weights derived from the general population. As the EQ-5D consists of simple questions and is not diseasespecific, it is used to evaluate HRQoL in various populations worldwide (14-17). The Korean national nutritional survey currently uses the EQ-5D, and a comparison between any population of interest and the Korean normative data is available.

Originally, the EQ-5D answers in each

dimension consisted of 3 levels: no, moderate, and extreme. Recently, the EuroQoL developed the EQ-5D-5L to overcome several limitations; this version, the answers consist of 5 levels. The EQ-5D-5L performs better in terms of lower ceiling effect and more discriminatory power (18-20). However, until recently, only a limited number of studies used the EQ-5D-5L.

Here, we investigated the HRQoL that was conducted using the EQ-5D-5L in Korean patients with pSS who were enrolled in a well-characterised prospective cohort and compared it with that in the Korean general population. Further, we aimed to identify the specific pSS features that determine the HRQoL in these patients.

Subjects and methods

Study population

All the enrolled patients with pSS in this study were Korean Initiative Sjögren's Syndrome (KISS) participants. The KISS was founded in 2013, with the aims of establishing a nationwide prospective cohort that contains overall clinical data and samples from patients with pSS and developing diagnostic and treatment tools for pSS. Informed consent was obtained from all patients according to the principles of the Declaration of Helsinki. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital (KC13ONMI0646). All data were collected and managed with the use of the Clinical Research and Trial Management System (Korea National Institutes of Health, Korea Centres for Disease Control and Prevention). Recruitment began in Seoul St. Mary's Hospital, a tertiary care university hospital and referral centre in Seoul, Korea, in October 2013. By April 2015, the database included 178 pSS patients from Seoul St. Mary's hospital. Patients were diagnosed with pSS according to the American-European Consensus Group criteria for pSS (21) or the 2012 American College of Rheumatology criteria (22).

EQ-5D

The EQ-5D assesses 5 different dimensions of health (mobility, self-care, usual activities, pain/discomfort, and

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Table I. Demographic and clinical characteristics of patients in the KISS study.

Age (yr)	55	(47–60)
Sex	1// Ien	(0, 41, 4, 84)
Disease duration (yr)	2.12	(0.41 - 4.64)
BMI (kg/m²)	22.5	(20.0-24.2)
ESSDAI	3	(1-6)
SSDDI	3	(2-3)
ESSPRI	5	(4–6.3)
Fatigue	5	(4–7)
Pain	3	(0-5)
Dryness	7	(5–9)
PGA	63	(49-79.25)
OSDI	38	(20–53)
Xerostomia inventory	37	(30-43)
Schirmer's test (mm/5 min)	4.5	(2–7)
Unstimulated salivary flow rate (mL/15 min)	0.3	(0–1.2)
Autoantibodies		
Anti-Ro or La	162	(91.0%)
RF	118	(67.4%)
ACPA	15	(8.6%)
Extraglandular manifestation	1	
Arthralgia/arthritis	80	(46.2%)
Raynaud's phenomenon	32	(18.5%)
Cutaneous vasculitis	23	(13.3%)
Pulmonary involvement	10	(5.8%)
Peripheral neuropathy	17	(9.8%)
Autoimmune thyroid disease	25	(14.5%)

Data are presented as median values and IQRs (25th and 75th) or percentages. KISS: Korean Initiative Sjögren's Syndrome; BMI: body mass index; ESSDAI: EULAR Sjögren's syndrome disease activity index; SSDDI: Sjögren's syndrome disease damage index; ESSPRI: EULAR Sjögren's syndrome patient-reported index; PGA: patient global assessment; OSDI: ocular surface damage index; RF: rheumatoid factor; ACPA: anti-CCP antibody.

anxiety/depression). Each dimension is scored based on the 5 possible responses of no, some, moderate, severe, and extreme problems, corresponding to scores 1-5, respectively. The score consists of 5 digits for the 5 domains describing a 'health state' (ex. 31534), and each of the possible 3125 states is mapped to a single "time trade-off" value derived from the South Korean reference data (23). The utility value ranges from 0 to 1, where 0 means death and 1 means a perfect health. A value with less than 0 can be calculated from the equation obtained from the object population, which stands for a status worse than death. For example, '31534' is converted into '0.4596' according to the South Korean reference data. Each individual's perception of their health was also recorded using a VAS with possible scores of 0-100, where 0 was the "worst imaginable health state" and 100 was the "best imaginable health state".



Statistical analyses

Statistical analyses were performed using the GraphPad Prism for the Windows software package (v. 4; GraphPad Software, San Diego, CA, USA). As many of the clinical parameters were not normally distributed, continuous variables were expressed as median and interquartile ranges (IQRs). Differences in the EQ-5D utility values between the KISS patients and the Korean general population were determined using the Student's t-test. Categorical variables were compared using the chi-square test. Bivariate correlation was determined using the Spearman correlation. Linear regression analysis was used to determine the predictors for the EQ-5D utility values. Age and sex were included in all the regression models. For mutiple linear regression analysis, stepwise selection method was used to determine independent preditors for the EQ-5D values. A value of p < 0.05 was taken to indicate statistical significance.

Results

Clinical and laboratory

characteristics of the subjects The characteristics of the patients are summarised in Table I. Among the 178 patients, 177 patients were women. The median age of the patients was 55 years, and the median disease duration was 2.12 years. The anti-Ro antibody was detected in 162 (91%) patients, and the rheumatoid factor (RF) was positive in 118 (67.5%) patients. The most common extraglandular symptom was arthralgia (80/178 [46.2%]).

EQ-5D utility values in patients with pSS The EQ-5D utility values ranged from 0.324 to 1.000 (Fig. 1A). The mean utility value in the patients with pSS was 0.773; this was significantly lower than 0.944, the value in the Korean general population (24). The proportions of subjects with problems in the 5 dimensions were 40.4% (mobility), 3.9% (self-care), 37.6% (usual activities), 78.7% (pain), and 70.2% (anxiety/depression). These data were significantly different compared to the corresponding data in the Korean general population: 12.5% (mobility), 2.7% (self-care), 9.8% (usual activities), 28.8% (pain), and 24.2% (anxiety /depression) (Fig. 1B).

Correlation between pSS features and the EQ-5D utility values

To identify the specific clinical features of pSS that are associated with HRQoL in patients with pSS, bivariate correlation analysis was performed. As shown

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Table II. Multiple linear regression models of EQ-5D utility values and candidate predictors.

	Indiv	Individual predictors			Multiple regression		
Predictor	Coefficient β	<i>p</i> -value	\mathbb{R}^2	Coefficient β	p-value	adjusted R ²	
ESSPRI	-0.055	< 0.001	0.208	-0.053	< 0.001	0.228	
Pain	-0.032	< 0.001	0.180				
Fatigue	-0.031	< 0.001	0.130				
OSDI	-0.003	< 0.001	0.092				
PGA	-0.003	< 0.001	0.103				
XI	-0.005	0.002	0.055				
Dryness	-0.024	0.001	0.063				

All regression coefficients are reported after adjustment for age and sex differences; age and sex are included in the model. ESSPRI: EULAR Sjögren's syndrome patient-reported index; OSDI: ocular surface damage index; PGA: patient global assessment; XI: xerostomia inventory.

in Fig. 2, several clinical features were significantly correlated with the EQ-5D utility values. The ESSPRI was found to have the highest correlation coefficient (Spearman's R = -0.459, p < 0.001) and was followed by the pain VAS, fatigue VAS, ocular surface disease index (OSDI) score, patient global assessment (PGA), xerostomia inventory (XI), and dryness. Neither the systemic disease activity index, the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), nor the laboratory values, including C3, C4, immunoglobulin, ESR, and CRP correlated with the EQ-5D utility values. To identify the critical predictors among the parameters that were associated with the EQ-5D values, linear regression analysis was performed. The potential predictors adjusted for age and sex were subjected to linear regression models. Individual predictors which showed statistical significance (p < 0.05) were analysed using stepwise selection methods. As the utility values were not normally distributed, logit-transformed data were used in the regression analysis. Stepwise selection analysis revealed that the ESSPRI was an independent predictor of the EQ-5D values (coefficient $\beta = -0.053$, $R^2 = 0.228$) (Table II).

Discussion

The current study demonstrated that the EQ-5D utility values in patients with pSS are significantly lower than those in the general population and that the ESSPRI is an independent determinant of HRQoL in patients with pSS.

These results are consistent with those of a study by Cho et al. (12), which evaluated the HRQoL of Korean pSS patients and non pSS individuals with sicca symptoms. The authors demonstrated that the HROoL is lower in pSS patients than in controls, with the use of a generic tool, the SF-36. The ESS-PRI was an independent predictor only in pSS patients, and was considered as a good disease specific outcome for predicting the HRQoL of pSS patients. Additionally, pSS patients enrolled in the United Kingdom pSS registry (UKPSSR) were reported to have a reduced HRQoL that was evaluated using the EQ-5D compared to the UK general population (7), although the EQ-5D-3L was used in the study.

In addition to the disease-related parameters, we also analysed the associations among the EQ-5D values and demographic parameters. Generally, a low education level, low income, female gender, and older age were associated with a low HRQoL (25). However, that was not the case in our cohort. There was a trend of increase in the utility values according to rising incomes; however, statistical significance was not achieved (data not shown).

As application of the EO-5D is not restricted to any specific disease, it is possible to compare the HRQoL between different disease populations. For example, a comparison can be made between pSS and RA patients. Analysis of 225 Korean RA patients revealed that Korean RA patients reported a low HRQoL, with a mean utility value of 0.60, which is significantly lower than that of our pSS patients (24). In addition, a substantial number of RA patients had problems in the self-care dimension, while there was no difference in this dimension between pSS patients and the general population.

One of the major goals of our study was to determine the factors that contribute to the EQ5D utility score from among the various characteristics of pSS, and the ESSPRI was found to be a major determinant after adjusting for confounders. The ESSPRI score is the mean of the dryness, fatigue, and pain scores on the VAS. This patient-reported outcome correlates well with the ESSDAI (11) and appropriately predicts the HRQoL assessed with SF-36 in Korean pSS patients (12). Although each component of the ESSPRI was positively correlated with the EQ-5D utility values, the combination demonstrated the best prediction, which corroborates its relevance as a disease outcome as mentioned in a recent review (26).

Another interesting issue was whether there was a difference in the contribution of severity of ocular symptoms (represented by OSDI) and oral symptoms (represented by XI) to the HRQoL. Our data showed that the OSDI was more closely associated with the utility values. Although the data did not provide any conclusive information, rheumatologists should ensure that the ocular symptoms in pSS patients are well managed in order to improve their QoL.

Our study has several limitations. First, the number of subjects was relatively small. Second, direct comparison with a large, representative, general population sample was not allowed. As mentioned, we used the EQ-5D-5L to overcome the ceiling effect. However, the national nutritional survey in Korea currently uses the EQ-5D-3L, and we had to compare our data with 600 individuals representative of the Korean general population, who were recruited to the validation study and responded to the EQ-5D-5L (27). This raises the issue of representativeness; nevertheless, the utility values were comparable between individuals evaluated with the EQ-5D-5L and those evaluated with the EQ-5D-3L (27), which enhanced the strength of our data. Third, consistent with previous reports (7, 8), depression is prevalent in pSS patients, with more than two-thirds of patients in the KISS study reporting some problems in the anxiety/depression domain. Unfortunately, our registry did not include any depression-specific questionnaire or index. The depression scale could have been included in the multiple linear regression model. In addition, it has to be mentioned that our conclusion is derived from intuitively expected results; it has been already reported that pSS patients have low quality of life and the symptoms-like pain, dryness, and fatigue may well affect the QoL. However, we believe our study has the strength that it demonstrated the concept by using a widely-used EQ-5d and made direct comparison with other population possible. And it was also confirmed that the composite of symptom scales best explained the HRQoL at least in Korean pSS patients.

As our data were derived from a prospective cohort, the clinical and laboratory data were well-characterised with few, if any, missing values. More-over, as the patients undergo follow-up checks of clinical and laboratory features as well as the EQ-5D questionnaire, we will be able to evaluate the change in the EQ-5D values and the possible association with other parameters and effects of medication. That would serve as an interesting topic for future research. In conclusion, the HRQoL of pSS patients is significantly lower than that of the general population, and the ESSPRI is an independent predictor of HRQoL in pSS patients.

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