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Pain and fatigue are predictors of quality of life in primary Sjögren's syndrome

Laiza Hombre Dias[1,2], Samira Tatiyama Miyamoto[3], Raquel Altoé Giovelli[2,4], Caerê Iamonde Maciel de Magalhães[5] and Valeria Valim[1,2,6*]

Abstract

Background: Few studies have evaluated the relation of quality of life (QoL) with symptoms and disease activity in primary Sjögren's syndrome (pSS). There is also scant information on the predictors of QoL in this population. The aim of this study was to assess QoL in patients with pSS and to investigate their possible predictors.

Methods: In a cross-sectional study, 77 patients with pSS were evaluated using the following questionnaires: Functional Assessment of Chronic Illness Therapy Fatigue Subscale (FACIT-Fatigue), EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), Short Form-36 Health Survey (SF-36) and World Health Organization Quality of Life Assessment (WHOQOL-BREF). Seventy-seven healthy controls responded to the SF-36 and WHOQOL-BREF. The Mann-Whitney test, t-test, Pearson and Spearman correlation, and multiple regression analysis were used in the statistical analysis.

Results: Patients with pSS and healthy controls were matched by gender and age. The mean scores for the ESSDAI, ESSPRI and FACIT-Fatigue were 3.34 ± 4.61, 6.58 ± 2.29 and 26.17 ± 11.02, respectively. Patients had a lower employment rate (36.4% versus 62.3%, $p < 0.01$) and higher work disability (10.4% versus 1.3%, $p < 0.01$). SF-36 and WHOQOL-BREF values were lower in patients with pSS ($p < 0.001$), except in the WHOQOL-BREF environment domain. Pain (ESSPRI), fatigue (FACIT-Fatigue), antinuclear antibody (ANA), anti-Ro-SSA and economic class (Brazilian Economic Classification Criteria - CCEB) were independent predictors of QoL.

Conclusions: The main predictors of poor QoL in patients with pSS were pain and fatigue, and these symptoms had an impact regardless of disease activity, age, schooling, marital status, work disability and fibromyalgia.

Keywords: Sjögren's syndrome, Quality of life, Pain, Fatigue

Introduction

Primary Sjögren syndrome (pSS) is an autoimmune, chronic and systemic disease that causes an inflammatory lymphocyte infiltrate with dysfunction of the salivary and lacrimal glands, leading to xerostomia and xerophthalmia. Epigenetic mechanisms such as DNA demethylation in epithelial cells and altered expression of microRNAs in salivary glands act on genetically susceptible patients, leading to the production of pathogenic autoantibodies [1]. Primary Sjögren syndrome affects mainly Caucasian women in the 4th to 5th decade of life and presents a broad clinical spectrum, with extraglandular manifestations occurring in more than two-thirds of cases, the most common being arthralgia or arthritis, Raynaud's phenomenon, skin vasculitis, interstitial pneumonitis and pulmonary fibrosis, peripheral neuropathy, and tubulointerstitial and glomerular nephritis [2–4].

Fatigue, a physical or mental feeling of tiredness, also affects approximately 70% of these patients and is strongly associated with psychosocial factors, occupational dysfunction and a greater number of medical visits but not with sicca severity or laboratory features [5, 6].

* Correspondence: val.valim@gmail.com
[1]Department of Clinical Medicine, Cassiano Antonio Moraes University Hospital / EBSERH, Federal University of Espírito Santo (Ufes), Av. Marechal Campos, 1468, Maruípe, Vitória, ES CEP: 29075-910, Brazil
[2]Brazilian Society of Rheumatology, São Paulo, Brazil
Full list of author information is available at the end of the article

In pSS, pain can be explained by different reasons, such as arthritis, pain amplification, and neuropathy. Arthritis is usually symmetrical, predominantly in peripheral and small joints, and may precede or appear simultaneously with sicca symptoms. Small-fiber neuropathy is the most common cause of neuropathic pain and is characterized by distal paraesthesias, allodynia, and burning and itching sensations. Half of the pSS patients present widespread pain, and combined with fatigue and sleep disorders, the diagnosis of associated fibromyalgia may be considered [7].

PSS patients have low quality of life (QoL) in the physical, emotional and social dimensions evaluated by different instruments, such as the Short Form-36 Health Survey (SF-36), the *World Health Organization Quality of Life – BREF* (WHOQOL-BREF) and the EuroQol 5-dimensions (EQ-5D) [8–20]. There is also an increase in health expenditures, both individual and social, and a higher frequency of work withdrawal in this population. QoL can be influenced by several factors, such as age, schooling and socioeconomic level [6, 9, 11, 12, 21].

Considering the aspects related to the disease itself, pain, fatigue and dryness are associated with worse QoL [11–13, 16, 17, 19, 22]. Comorbidities such as depression, anxiety, and fibromyalgia are also negatively correlated [11, 18]. The association with immunological and biological variables is controversial or weak. Hypergammaglobulinemia, the presence of anti-SSA/Ro, anti-SSB/La antibodies, antinuclear antibody (ANA) or rheumatoid factor (RF), cytopenias, high cytokine levels or salivary gland biopsy do not correlate with worse QoL, while extraglandular manifestations, mainly articular and pulmonary, are poorly correlated [13]. Few studies have evaluated the relationship of QoL with symptoms and disease activity as measured by EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) and EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) [17, 19]. There is also little information on the predictors of QoL in this population [11, 17, 19].

The objective of this study was to evaluate whether disease activity or symptoms such as pain, dryness, and fatigue are predictors of QoL regardless of other clinical-epidemiological features in patients with pSS.

Methods

A cross-sectional study was conducted from January to July 2013 at the University Hospital of Federal University of Espírito Santo (HUCAM), in Vitória, Brazil.

PSS patients who met the American – European classification criteria (AECG) [23] and signed the informed consent form (ICF) were included. Secondary Sjögren's syndrome patients were excluded.

The control group consisted of healthy individuals matched by gender and age who were in external circulation areas of the hospital, as well as donors from the blood bank. The exclusion criteria were having autoimmune rheumatic disease at < 18 years of age and any other comorbidity. All patients signed the ICF. The Research Ethics Committee (REC) of HUCAM, protocol number 178.520, approved the project on January 30, 2013.

Demographic data such as age, gender, self-reported color, level of schooling, income by the Brazilian Economic Classification Criteria (CCEB) [24], labor status, work disability (sick leave or early retirement), as well as clinical data such as diagnosis of fibromyalgia (American College of Rheumatology - ACR 1990 or ACR 2010) [25, 26], salivary gland biopsy, presence of antinuclear antibodies (ANA), rheumatoid factor (RF), anti-SSA/Ro and anti-SSB/La were collected from medical records and physician interview.

Minor salivary gland biopsies were performed and analyzed by rheumatologists and pathologists with experience in pSS and were considered positive when the histopathology showed one or more lymphocytic infiltrates with more than 50 mononuclear cells in an area of 4 mm^2 [24]. The anti-SSA/Ro and anti-SSB/La laboratory tests were performed by the hemagglutination technique, while ANA was performed by indirect immunofluorescence and RF by the latex test.

To evaluate the activity of the disease, two physicians experienced in pSS applied the ESSDAI. It has 12 domains of systemic evaluation (constitutional, lymphadenopathy, glandular, articular, cutaneous, respiratory, renal, muscular, peripheral and central nervous system, hematological and biological). The domains have different weights in the final score, 0 to 123, according to the level of activity [27, 28]. Values lower than 5 are considered to indicate low disease activity; values from 5 to 13, moderate activity; and values greater than or equal to 14, high activity [29].

Symptoms and QoL were assessed using self-administered questionnaires, and a trained professional was available to assist participants when needed. PSS patients answered the ESSPRI, which measures three symptoms related to the disease: dryness, pain and fatigue. Each domain ranges from 0 to 10, and the result is the average of the three domains [30]. Values less than 5 are considered acceptable [29].

Fatigue in pSS patients was evaluated through the Functional Assessment of Chronic Illness Therapy - fatigue (FACIT-fatigue). The FACIT system originally developed to evaluate QoL in cancer patients has been widely used in several chronic diseases. Its score ranges from 0 to 52, and its value is inversely proportional to the degree of fatigue [31].

The SF-36 and WHOQOL-BREF questionnaires were used to assess QoL in pSS patients and healthy controls. The SF-36 is an easy-to-administer instrument

consisting of 36 items divided into 8 domains: physical functioning, physical role functioning, bodily pain, general health, vitality, social functioning, emotional role functioning and mental health. These can be grouped into two components that summarize the dimensions: physical (PCS) and mental (MCS) component summaries. Its final score ranges from 0 to 100, and the higher the score, the better the overall health condition [32]. Developed by the World Health Organization (WHO), the WHOQOL-BREF is an abbreviated version of the WHOQOL-100. It is composed of 26 questions. The first two questions are general QoL issues, and the remaining 24 facets will form four domains: physical, psychological, social relations and environment. The total score ranges from zero to 100, and the higher its value, the better the QoL [33, 34].

The chi-square, Fisher and likelihood ratio association tests were used for qualitative variables among patients with pSS and healthy controls. The Kolmogorov-Smirnov test was used to evaluate the normal distribution of the data. For quantitative variables, the Mann-Whitney test was used when there was a breakdown of normality, and with normal data, the t test was used. Pearson or Spearman tests were used in the correlations. To identify independent predictors for quality of life, stepwise linear regression analysis was performed. The variables considered in the analysis were age, weight, body mass index (BMI), smoking, alcoholism, marital status, schooling, fibromyalgia, CCEB, work disability (sick leave or early retirement), ESSDAI, ESSPRI, FACIT-Fatigue, salivary gland biopsy, ANA, anti-SSA/Ro, anti-SSB/La and RF. Variables with a statistical significance level of 10% were included in the multiple regression analysis. Statistical significance was set at a p value of ≤0.05. The Statistical Package for the Social Sciences (SPSS), version 20.0, Armonk, New York (NY), 2011 software was used.

Results

Of 127 pSS outpatients, 27 were excluded because they did not meet the AECG, and 33 were not willing to participate.

Seventy-seven pSS patients and 77 healthy women were included, aged 27 to 67 years. Groups were similar in age, ethnicity, schooling, marital status and economic classification. Patients had a lower employment rate (36.4% versus 62.3%, $p < 0.01$) and higher work disability (10.4% versus 1.3%, $p < 0.01$). Moreover, the patients had a low disease activity (ESSDAI 3.34 ± 4.61) and a low frequency of autoantibodies, characterizing a sample with mild disease. Biological and articular domains were the most frequently affected. In contrast, the patients presented a high level of symptoms (ESSPRI 6.58 ± 2.29). Among patients with pSS, the percentage of fibromyalgia was 42.9% (Table 1).

Table 1 Demographic and clinical data in pSS patients and healthy controls

	pSS ($n = 77$)	Controls ($n = 77$)
Age, mean, years	52.34 (9.03)	52.27 (8.91)
Ethnicity		
Black (%)	11.7	13
Brown (%)	59.7	49.4
White (%)	24.7	37.7
Indigenous (%)	2.6	0
Education		
< 8 years (%)	50.7	57.2
≥ 8 years (%)	48.1	40.3
Never studied (%)	1.2	2.5
Marital status		
Married (%)	66.2	63.6
Not married (%)	14.3	13
Divorced/widow (%)	19.5	23.4
CCEB		
A (%)	1.3	0
B (%)	23.4	26.6
C (%)	52	49.3
D (%)	18.2	24
E (%)	0	0
*Employment rate (%)	36.4	62.3
Work disability (%)*	10.4	1.3
Positive salivary biopsy (focus score ≥ 1) (%)	90.5	
Anti-SSA/Ro (%)	33.3	
Anti-SSB/La (%)	24	
Antinuclear antibody (%)	68.9	
Rheumatoid factor (%)	29.2	
Fibromyalgia (%)	42.9	
FACIT-*Fatigue,* mean, SD	26.17 (11.02)	
ESSPRI, mean, SD	6.58 (2.29)	
Fatigue, mean, SD	6.38 (2.57)	
Dryness, mean, SD	6.53 (2.78)	
Pain, mean, SD	6.84 (3.12)	
Extra glandular manifestations (%)	49.4	
ESSDAI, mean SD	3.34 (4.61)	

pSS Primary Sjögren Syndrome, *CCEB* Brazilian Economic Classification Criteria, *FACIT* Fatigue – Functional Assessment of Chronic Illness Therapy-Fatigue, *SD* standard deviation, *ESSPRI* EULAR Sjögren's syndrome patient reported index
*$p < 0.01$

The QoL measured by SF-36 and WHOQOL-BREF was worse in patients with pSS than in healthy controls, except for the environment domain tested by WHOQOL-BREF, which was similar for both groups (Table 2).

Table 2 Comparison of quality of life between pSS patients and healthy controls

SF-36	pSS ($n = 77$)	Controls ($n = 77$)
*Physical functioning	37.3 ± 24.2	80.5 ± 20.8
*Physical role functioning	27.6 ± 35.9	73.4 ± 37.2
*Bodily pain	36.7 ± 22.2	69.5 ± 21.4
*General health	43.2 ± 17.9	69.5 ± 20.0
*Vitality	37.2 ± 20.6	64.8 ± 20.9
*Social functioning	48.3 ± 26.9	74.8 ± 23.1
*Emotional role functioning	31.1 ± 38.6	69.3 ± 40.0
*Mental health	46.2 ± 22.3	67.8 ± 23.0
*PCS	33.1 ± 9.1	48.9 ± 8.5
*MCS	37.2 ± 11.4	46.8 ± 12.3
WHOQOL-BREF		
*Physical health	41.6 ± 16.8	67.7 ± 16.8
*Psychological health	53.4 ± 18.8	63.9 ± 15.9
*Social relations	55.5 ± 22.0	65.4 ± 18.2
Environment	49.1 ± 12.7	53.0 ± 16.5

SF-36 Short Form 36 Health Survey, *pSS* primary Sjögren's Syndrome, *PSC* Physical Component Summary, *MCS* Mental Component Summary, *WHOQOL-BREF* World Health Organization Quality of Life Assessment
*$p < 0.01$

Table 3 Comparison of quality of life between patients with acceptable and non-acceptable ESSPRI

	ESSPRI	
	Acceptable	Non-acceptable
SF36		
*Physical functioning	63.44 ± 29.08	30.83 ± 17.54
Physical role functioning	35.94 ± 43.75	25.00 ± 33.19
*Bodily pain	55.06 ± 25.69	31.80 ± 18.56
*General health	53.75 ± 19.21	40.57 ± 16.66
Vitality	47.19 ± 34.92	34.92 ± 18.31
Social functioning	54.66 ± 47.02	47.02 ± 27.27
**Emotional role functioning	52.08 ± 25.00	25.00 ± 34.51
**Mental health	56.00 ± 24.57	43.87 ± 21.05
*PCS	40.21 ± 10.88	31.28 ± 7.62
MCS	40.83 ± 13.14	36.31 ± 10.84
WHOQOL-BREF		
*Physical health	56.70 ± 19.25	37.54 ± 13.76
**Psychological health	63.02 ± 16.66	50.90 ± 18.75
*Social relations	71.35 ± 14.58	51.11 ± 21.94
**Environment	54.88 ± 9.20	47.53 ± 13.23

ESSPRI EULAR Sjögren's syndrome patient reported index, *SF-36* Short Form-36 Health Survey, *PCS* Physical Component Summary, *MCS* Mental Component Summary, *WHOQOL-BREF* World Health Organization quality of life – BREF
*$p < 0.01$; **$p < 0.05$

In the pSS group, patients with a nonacceptable ESSP RI (≥ 5) had all WHOQOL-BREF and most SF-36 domains worse than patients with an acceptable ESSPRI (Table 3). Patients with pSS and fibromyalgia had worse QoL values in bodily pain (SF-36) and physical health (WHOQOL-BREF) (Table 4).

There was a moderate-to-strong correlation of FACIT-Fatigue with all domains of QoL questionnaires. The ESSPRI also correlated with all QoL domains. The ESS-DAI showed only a weak correlation with the emotional role functioning domain of the SF-36 and did not correlate with fatigue indexes (FACIT-Fatigue) and ESSPRI (Table 5).

In the regression analysis, pain (ESSPRI), fatigue (FACI T-Fatigue), antinuclear antibody (ANA), anti-Ro-SSA and economic class (Brazilian Economic Classification Criteria - CCEB) were independent predictors of QoL. The symptoms measured by FACIT-Fatigue and ESSPRI pain were the main predictors of poor QoL, regardless of age, marital status, schooling, work disability, disease activity and fibromyalgia. In the PCS of the SF-36, the predictors for the worst values were pain, fatigue, and the presence of ANA and anti-SSA/Ro autoantibodies. Fatigue was the only predictor in the MCS of the SF-36 and psychological health domain of the WHOQOL-BREF. Pain interfered with the PCS of the SF-36, physical health, social relations and environmental domains of the WHOQOL-BREF (Table 6).

Table 4 Comparison of QoL between pSS patients with fibromyalgia

		Fibromyalgia	
		Yes	No
SF-36	Physical functioning	30.9 ± 18.9	42.6 ± 26.5
	Physical role functioning	22.0 ± 30.5	32.4 ± 39.1
	*Bodily pain	25 ± 15.3	45.6 ± 22.4
	General health	37.9 ± 17.2	47.4 ± 17.4
	Vitality	30.9 ± 17.4	42.2 ± 21.4
	Social functioning	42.3 ± 25.2	53.7 ± 27.7
	Emotional role functionig	28.3 ± 38.3	34.1 ± 39.0
	Mental health	41.7 ± 22.7	49.6 ± 21.4
	PCS	29.7 ± 6.5	35.8 ± 9.8
	MCS	35.7 ± 11.6	38.6 ± 11.1
WHOQOL-BREF	*Physical health	35.5 ± 15.3	46.2 ± 16.5
	Social relations	51.0 ± 23.0	58.9 ± 20.9
	Environment	45.6 ± 11.4	51.8 ± 13.1
	Psychological health	48.7 ± 19.3	56.8 ± 17.8

QoL Quality of Life, *pSS* primary Sjögren's Syndrome, *SF-36* Short Form 36 Health Survey, *PSC* Physical Component Summary, *MCS* Mental Component Summary, *WHOQOL-BREF* World Health Organization Quality of Life Assessment
*$p < 0.01$

Table 5 Correlation of quality of life, disease activity, symptoms and fatigue

	ESSDAI	ESSPRI dryness	ESSPRI fatigue	ESSPRI pain	ESSPRI Total	FACIT-Fatigue
SF36						
Physical functioning	0.04	−0.44**	−0.29*	− 0.55**	− 0.56**	0.53**
Physical role functioning	0.01	−0.17	−0.08	− 0.23*	−0.24*	0.35**
Bodily pain	0.03	−0.33**	−0.23*	− 0.59**	−0.53**	0.56**
General health	−0.08	−0.27*	− 0.17	−0.34**	− 0.34**	0.56**
Vitality	−0.04	−0.23*	− 0.26*	−0.36**	− 0.39**	0.56**
Social functioning	−0.01	−0.33**	− 0.18	−0.21	− 0.29*	0.45**
Emotional role functioning	−0.24**	−0.31**	− 0.11	−0.23	− 0.29*	0.48**
Mental health	0.04	−0.21	−0.23*	− 0.31**	−0.28*	0.46**
PCS	0.06	−0.35**	−0.21	− 0.53**	−0.5**	0.46**
MCS	−0.14	−0.2	− 0.17	−0.12	− 0.24*	0.48**
Whoqol Bref						
Physical health	−0.09	−0.34**	− 0.19	−0.43**	− 0.50**	0.68**
Psychological health	−0.08	−0.32**	− 0.19	−0.36**	− 0.38**	0.56**
Social relations	−0.03	−0.17	− 0.2	−0.34**	− 0.33**	0.37**
Environment	−0.01	−0.19	− 0.18	−0.49**	− 0.34**	0.32**
ESSDAI		−0.11	−0.01	− 0.04	−0.08	− 0.06

ESSDAI EULAR Sjögren's syndrome disease activity index, *ESSPRI* EULAR Sjögren's syndrome patient reported index, *FACIT* Fatigue – Functional Assessment of Chronic Illness Therapy-Fatigue, *SF-36* Short Form-36 Health Survey, *PCS* Physical Component Summary, *MCS* Mental Component Summary, *WHOQOL-BREF* World Health Organization quality of life – BREF
*$p < 0.01$; '**$p < 0.05$

Discussion

Here, PSS patients were found to have lower QoL scores than healthy controls, corroborating previous studies in other countries [11–13, 15–19, 22]. The relevance of the present data was to demonstrate that symptoms, but not disease activity, were the main predictors of low QoL.

Few studies have performed multivariate analyses to identify predictors of QoL in pSS. Cornec et al. corroborated the results of our study, showing that disease activity is not associated with greater QoL impairments in 120 French patients with moderate-to-high levels of systemic activity, despite the low level of disease activity in our patients [35]. Disease activity (ESSDAI) was also not a predictor of QoL in 639 pSS patients from United Kingdom (UK) [18] and in 104 Korean patients [17]. In contrast, Omma et al. found that the ESSDAI was an independent determinant of all SF-36 domains, with the exception of the vitality domain, in 105 patients from Turkey, most of whom had low to moderate levels of disease activity [36]. As in Liu et al.'s study [37], our results showed that pain and fatigue were independently associated with a low physical component summary (PCS) of the SF-36 and that fatigue was associated with a low mental component summary (MCS) of the SF-36. In the Cornec et al. study, only pain was associated [35]. Omma et al. demonstrated that the ESSPRI was an independent determinant of bodily pain, general health, mental health and PCS of the SF-36, while fatigue was

Table 6 Predictors of quality of life

	SF-36		WHOQOL-BREF									
	PCS R^2: 0.56		MCS R^2: 0.22		Physical health R^2: 0.52		Psychological health R^2: 0.36		Social relations R^2: 0.23		Environment R^2: 0.30	
	ß	*p*-value	ß	*p*-value	ß	*p*-value	ß	*p*-value	ß	*p*-value	ß	*p*-value
ESSPRI-pain	−1.16	0.00			−1.48	0.00			−1.53	0.06	−1.63	0.00
FACIT-Fatigue	0.31	0.00	0.51	0.00	0.88	0.00	1.00	0.00	0.48	0.04		
ANA	−4.64	0.01										
Anti-SSA/Ro	−4.09	0.01										
CCEB									− 4.91	0.05	−3.9	0.01

SF-36 Short Form-36 Health Survey, *WHOQOL-BREF* World Health Organization quality of life – BREF, *PCS* Physical Component Summary, *MCS* Mental Component Summary, *ANA* Antinuclear Antibody, *CCEB* Brazilian Economic Classification Criteria

significantly correlated with four or more domains of the SF-36 [36].

Results showed a correlation between the ESSDAI only and the emotional aspects domain of the SF-36, and yet this correlation was weak, not being confirmed as a predictor of QoL in patients with pSS. Sharing a similar result, a cohort in the UK using the EQ-5D to assess QoL demonstrated a weak correlation with the ESSDAI [19]. Yacoub et al. used the degree of activity in salivary gland biopsy, immunological status and severity of systemic involvement as a way of assessing disease activity, and they found no correlation with QoL or fatigue [13]. It is not clear why there is a weak association between disease activity (ESSDAI) and QoL. One possible answer could be the wide range of ESSDAI scores (0–123) in samples with low mean activity. In addition, ESSDAI is an index that does not assess established damage, only current activity; thus, perhaps the patient's perception about the QoL is not modified at that moment, but when there is an established organic dysfunction. Other studies correlating injury rates with disease activity and QoL could better elucidate the issue.

QoL was worse in patients with higher nonacceptable ESSPRI, and it was not associated with ESSDAI, corroborating that symptoms (fatigue, pain and dryness) impact QoL more than disease activity.

In pSS, QoL has been found to be associated with fatigue, pain/articular involvement, ocular and oral involvement, pruritus, sexual dysfunction, impaired sleep, pulmonary manifestations, psychological dysfunction and impaired physical function [20]. On the other hand, delayed diagnosis, protracted course of the disease, and the lack of social support are also causes of the decline in the quality of life in these patients [37].

Fatigue is considered a hallmark of pSS [5]. In the present study, fatigue (FACIT-fatigue) was strongly associated with all dimensions of QoL and was an independent risk factor for the physical and mental aspects of QoL in both instruments, SF-36 and WHOQOL-BREF. In contrast, there was no association between fatigue and disease activity measured by the ESSDAI. Taken together, the results suggest that fatigue is itself associated with pSS but may not be explained by disease activity.

Recent evidence has shown weak or no association with inflammatory biomarkers such as interleukin (IL)-1b, IL-2, IL-6, IL-10 and tumor necrosis factor alpha (TNF-α). In the same direction, immunosuppressors and biological therapy failed to treat fatigue in pSS [38]. However, Howard et al. showed that lower levels of the pro-inflammatory cytokines inducible protein (IP)-10 and interferon-gamma (IFN-γ), together with pain and depression, were the most important predictors of fatigue [39], and Davies et al. demonstrated that TNF-α and LT-α have an inverse relationship with fatigue severity in pSS [40]. A proteomic study of cerebrospinal fluid showed that some proteins that are increased in pSS have a role in the downregulation of inflammation and in the cellular stress defense (hemopexin, pigment epithelium-derived factor, clusterin, osteopontin, and selenium-binding protein 1). These results suggest that some fatigue signaling pathways are associated with "cellular protection and defense" and are not directly related to proinflammatory factors [41]. Nonetheless, the evidence for an association between fatigue and disease activity – or any other inflammatory markers – remains controversial.

In fact, the pathogenesis of fatigue in pSS is unknown but seems to be associated with a lower aerobic capacity and lower physical activity levels, sleep disturbances, autonomic dysfunction, depression, psychological profiles, and fibromyalgia [38]. It is noteworthy that, in the multiple regression models, fatigue measured by FACIT-Fatigue was the only predictor of the MCS of SF-36 and the psychological component of WHOQOL-BREF. These data indicate that this symptom impacts not only the physical aspects but also the mental health of these individuals. Other studies have pointed to depression as an important determinant of poor QoL along with fatigue in these patients [11, 17, 18], which could partially explain the low values of the determination coefficients in the mental domain of the SF-36, as well as in the psychological, social relations and environmental domains of the WHOQOL-BREF. However, we did not evaluate psychiatric disorders, such as depression or anxiety, which is a limitation of this study. Interestingly, aerobic exercise has been found to improve fatigue, but not QoL and depression [42], and resistance exercise has been found to improve QoL [43]. Clearly, many efforts still need to be made to elucidate the pathogenesis of fatigue, as well as to identify pharmacological and nonpharmacological therapies to treat fatigue and improve the QoL in pSS.

Pain was a determinant for lower QoL in the physical, social relations and environmental domains but not for mental aspects. A large proportion of patients with pSS have noninflammatory musculoskeletal pain without the laboratory or clinical abnormalities of arthritis. Among patients with pSS, cases of pain amplification syndrome are associated with a benign pole of the disease, with a low frequency of autoantibodies and extraglandular manifestations [44].

The prevalence of fibromyalgia in pSS varies from 12 to 55% [7]. In our study, the prevalence was 42.9%. This large range can certainly be explained by the various criteria to diagnose fibromyalgia as well as pSS that have been applied over time. Indeed, pain and fatigue are common symptoms in both fibromyalgia and pSS, and the association of the two can be a misleading factor.

However, in the present study, fatigue and pain were the main predictors of poor QoL, regardless of the diagnosis of fibromyalgia, indicating that pSS itself was associated with poor QoL. Lendrem et al. found no difference in QoL between those with fibromyalgic symptoms and those without [18]. Notwithstanding, our study did not investigate other factors, such as subclinical autonomic dysfunction and sleep disorders, that could contribute to pain and fatigue in these patients with pSS without fibromyalgia [45].

The present study demonstrated a contribution of ANA and Anti-Ro/SSA, even if discrete, to worse values in the SF-36 physical domain. This information differs from the findings of other studies in which no correlation was found between antibodies and QoL [9, 13, 18]. However, it is well established in the literature that patients with positive autoantibodies evolve to greater glandular dysfunction and systemic manifestations [46, 47].

Although dryness is the main symptom and causes great discomfort in pSS patients, it was not a predictor of QoL, as demonstrated in previous studies [11, 35]. A review on QoL in pSS mentioned that it is possible this may reflect an inadequacy of single VAS scales, as is often used in such studies, to capture the breadth and impact of oral and ocular involvement. That review also showed that non-SS sicca syndrome patients have an impairment of QoL similar to that observed in pSS and other chronic diseases such as rheumatoid arthritis, systemic lupus erythematosus and fibromyalgia [20].

In the comparison between patients and healthy controls, SF-36 and WHOQOL-BREF domains were worse in patients with pSS, showing that the disease had a negative influence on the different aspects of QoL. Interestingly, the environmental domain, which is associated with transportation-related and residential conditions, in pSS was similar to that in healthy controls, probably because both groups showed similar socioeconomic levels.

Other relevant information included the lower number of employed individuals and the greater amount of sick leave among pSS patients compared to healthy controls. Patients with pSS also generate a higher cost to the health system, since they use more medical services, have higher hospitalization rates and use more medications [11, 20]. These data demonstrate how much the disease interferes not only emotionally and physically but also socially and individually, affecting employers and the government, increasing social security costs and reducing the life expectancy of the worker.

The study has limitations. Medications used by patients and other comorbidities were not collected. These data could have enriched the analysis, as some medications can yield adverse effects and other diseases may have symptoms with negative impacts on QoL. Questionnaires about emotional aspects such as depression and anxiety were also not applied, and these data could have improved the values of the mental domain determination coefficients.

Conclusion

This study demonstrated that the main predictors of poor QoL in patients with pSS were pain and fatigue, independent of disease activity, age, schooling, work disability, marital status and fibromyalgia.

Abbreviations

ANA: Antinuclear antibody; BMI: Body mass index; CCEB: Brazilian Economic Classification Criteria; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy Fatigue Subscale; pSS: Primary Sjögren's syndrome; QoL: Quality of life; RF: Rheumatoid factor; SF-36: Short Form-36 Health Survey; WHOQOL-BREF: World Health Organization Quality of Life Assessment

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Authors' contributions

All authors contributed to the conception and design of the study, analysis and interpretation of the data. In addition, all authors performed a critical review and read and approved the final version of this manuscript.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Clinical Medicine, Cassiano Antonio Moraes University Hospital / EBSERH, Federal University of Espírito Santo (Ufes), Av. Marechal Campos, 1468, Maruípe, Vitória, ES CEP: 29075-910, Brazil. [2]Brazilian Society of Rheumatology, São Paulo, Brazil. [3]Department of Integrated Health Education, Federal University of Espírito Santo (Ufes), Av. Marechal Campos, 1468, Maruípe, Vitória, ES CEP: 29075-910, Brazil. [4]Department of Clinical Medicine, School of Sciences of Santa Casa de Misericórdia de Vitória (Emescam), Av. Nossa Senhora da Penha 2190, Vitória, ES 29045-925, Brazil. [5]Federal University of Espírito Santo (Ufes), Av. Marechal Campos, 1468, Maruípe, Vitória, ES CEP: 29075-910, Brazil. [6]Brazilian Sjögren Syndrome Commission, São Paulo, Brazil.

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