

Work productivity and activity impairment in patients with primary Sjögren's syndrome

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ABSTRACT

Objective. In this observational, analytical, cross-sectional study we aimed to describe the impact of primary Sjögren's syndrome (pSS) on work productivity and activities of daily living (ADL) to assess the association between ADL impairment and clinical manifestations and to compare ADL impairment according to patients' socioeconomic condition.

Methods. Patients diagnosed with pSS attending 11 centres from Argentina were included. To evaluate work productivity and ADL impairment, a work productivity and activity impairment questionnaire (WPAI) was used. A multiple linear regression model was performed, considering deterioration on ADL due to health as a dependent variable, adjusted for potential confounders.

Results. 252 patients were included, 98.4% were women, with a mean age of 52.6 years (± 14.8). The average percentage of time lost due to health was 15.7 hours (± 30.1 95% CI: 9.6–21.9); the decrease in work productivity was 27.2 (± 30.2 95% CI: 21.3–33.1), the total disability was 33.7 (± 35.8 95% CI: 26.4–44) and ADL deterioration was 34.2 (± 30.9 95% CI: 30.4–38). In the multivariate analysis, xerostomia, arthritis and depression showed significant and independent association. The mean of ADL impairment was 38.2 (± 30.7) in patients attending public centres versus 28 (± 30.6) in private centres, which was a statistically significant difference.

Conclusion. We found a compromise in all WPAI domains. Arthritis, xerostomia and depression were associated significantly and independently with ADL impairment. Deterioration in ADL was greater in patients treated in public centres. Considering these aspects will allow a better understanding of patients who suffer from this disease.

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterised by an inflammatory process with lymphoplasmocytic infiltration, which mainly affects exocrine secretion glands, and can compromise other organs (1, 2). It is more frequent in women, with an approximate female/male ratio of 10/1, and between the ages 40–60 years (3).

The classic approach of pSS is based on symptomatic treatment for glandular manifestations and immunosuppressive and/or anti-inflammatory therapy for systemic manifestations. Moreover, glucocorticoids are commonly used in SS for glandular, joint, cutaneous, lung, haematological, renal and neurological involvement (4).

The presence of SICCA symptoms, fatigue, extra-glandular involvement, and the psychosocial impact of the disease can negatively affect the quality of life and work productivity (5-8).

Work performance is influenced by contextual factors, both of the worker and of the work environment, including physical, as well as psychological and social aspects (9), which are involved in this pathology.

In contrast to what has been observed in other rheumatic diseases, in which the deterioration of work productivity has been evaluated in a large number of studies (10), there is scarce information about this topic in patients with pSS.

It is important to consider that the Argentinian Health System is divided into 3 subsectors: public, private, and social security sectors. Low-income patients usually attend the public sector, while those with higher resources go to the private sector; for this reason, the site of care was considered a surrogate of the socioeconomic condition.

The objectives of this study were:

1. To describe the impact of pSS on work productivity and activities of daily living (ADL) using work productivity and activity impairment questionnaire (WPAI);
2. To evaluate the association between the presence of clinical manifestations and ADL impairment;
3. To compare work productivity and ADL impairment according to educational level and site of care (public or private centres), as surrogates for the socioeconomic condition.

Materials and methods

A multicentre, observational, analytical and cross-sectional study was performed. Patients diagnosed with pSS that meet American-European 2002 (11) and/or American College of Rheumatology (ACR)- European League against Rheumatism (EULAR) 2016 (12) treated at 11 rheumatology centres of Argentina, from private and public centres, between November 2013 and December 2016, were included. The patients were older than 18 years and expressed their agreement to participate in the study, signing an informed consent. Patients with diagnosis of another associated autoimmune rheumatic disease or other uncontrolled (active and not adequately treated) chronic diseases were excluded (heart, kidney and liver failure, liver cirrhosis, chronic lung disease, neuropsychiatric or dermatological uncontrolled disease, as well as diabetes, peripheral vascular disease, neoplasms (with the exception of lymphoma associated to pSS) and uncontrolled hypothyroidism, as well as transplant patients).

Dependent variables

Work productivity. Work productivity was measured by the Work Productivity and Activity Impairment Questionnaire: Global Health (WPAI-GH) (13) in its validated Spanish version for Latin America. This questionnaire measures the effect of health and the severity of symptoms on work and non-work activities, considering last week as the time frame. It consists of 6 questions: Q1: If the patient is working or not; Q2: number of lost working hours due to

health; Q3: number of work hours lost for another cause; Q4: number of hours actually worked; Q5: affected productivity at work using a scale from 0 to 10 (0 = did not affect work; 10 = completely prevented him from working); Q6: impairment of ADLs, using a scale from 0 to 10 (14). From these questions, four domains are obtained: absenteeism (lost work time due to health); presentism (disability at work due to health); total percentage of occupational disability due to health; and impairment in ADLs due to health.

The calculation of each domain is carried out as follows:

1. Percentage of time lost due to health: $[Q2/(Q2+Q4)] \times 100$.
2. Percentage of disability at work due to health: $(Q5/10) \times 100$.
3. Total percentage of occupational disability due to health: $[Q2/(Q2+Q4) + [(1-Q2)/(Q2+Q4)) \times (Q5/10)] \times 100$
4. Percentage of impairment on ADL due to health: $(Q6/10) \times 100$.

Results are expressed in percentages with higher values indicating greater disability and lower productivity (15).

Independent variables

Sociodemographic variables: sex, age at the time of evaluation, educational level, site of care, work activity.

Variables related to the disease: variables specifically related to the disease were evaluated:

1. Time of disease duration at the moment of evaluation: measured in years.
2. Xerosis and fatigue: the presence of xerophthalmia, xerostomia, xeroderma, xerovagina and fatigue were considered. Each of these items were measured through patient's visual analogue scales (VAS), from 0 to 100 mm, considering the last week as the time frame.
3. Systemic clinical manifestations: were considered of interest because they reflect the systemic activity of disease. The presence of the following clinical manifestations was determined: parotid swelling, arthralgia, arthritis, myalgia, Raynaud's phenomenon, polyneuropathy, cutaneous vasculitis, lung involvement

(if there was clinical suspicion and it was confirmed by high resolution chest tomography and functional respiratory examination with DLCO), lymphoma, kidney involvement (presence of glomerulonephritis diagnosed by biopsy or renal tubular acidosis confirmed by laboratory (complete form) or by bicarbonate test (incomplete form), chronic anaemia and neutropenia disorders. Manifestations that were present in the previous 4 weeks were recorded.

4. Treatment: the following variables were considered: treatment with artificial tears and/or ophthalmic gel, treatment with oral moisturiser, treatment with secretagogues, treatment with hydroxychloroquine, treatment with immunosuppressants.

Potential confounders

The presence of possible confounders was examined since they can negatively impact both work productivity and ADL. The presence of: depression (measured by the Spanish version of the Patient Health Questionnaire 9: PHQ-9 for Argentina) (16, 18), anxiety (measured by the Spanish version of the self-administered questionnaire Generalized Anxiety Disorder 7: GAD- 7 for Argentina) (16, 18). Other potential confounders such as osteoarthritis, fibromyalgia, smoking, alcoholism, arterial hypertension (evaluated by the the WHO STEPS questionnaire, Spanish version for Argentina) (19), and level of physical activity (evaluated by the International Physical Activity Questionnaire: IPAQ, Spanish version validated for Argentina) (20, 21) were also considered.

Ethical aspects

The project was approved by the Research Ethics Committees (REC) of the participating centres. This investigation complies with all pertinent laws and regulations, to which the RECs adhere, in force at the time of the execution of this investigation. Informed consent was obtained from participating patients. The confidentiality of personal information was respected, guaranteeing the non-use of the information obtained to the detriment of the study subjects.

Statistical analysis

A descriptive analysis of the general characteristics of the population, and domains of WPAI was performed. Continuous variables were reported as mean and standard deviation (SD) or median with interquartile range (IQR), according to their distribution and sample size. The categorical variables were reported in percentages. A multiple linear regression model was constructed considering deterioration in ADL as the dependent variable. The presence of differences in the work productivity domains according to educational level and site of care was evaluated, as surrogates for the socioeconomic condition; if differences were found, a multiple linear regression model was constructed with each of these variables as dependent variable. All analyses were performed using STATA 12 software.

Results

Sociodemographic variables

A total of 252 patients from 11 centres were included. Five of them were public centres and six were private. Regarding the sociodemographic characteristics of the population (Table I), 98.4% of patients were female, with a mean age of 52.6 years (SD ±14.8) and a mean time of disease duration of 7.3 years (SD ±7.5). 56.7% had completed secondary school level or had a higher level of education.

Variables related to disease

Xerosis and fatigue. Regarding xerosis, those reported as more intense were xerophthalmia (56.9±30.3) and xerostomia (56.7±31.1). The mean VAS of fatigue was 49.9 (±33.3). The results are summarised in Table II.

Systemic clinical manifestations

The most frequent systemic manifestation on the previous month of evaluation was arthralgia (53%). The remaining clinical manifestations are represented in Figure 1.

Treatment

Regarding treatment, 87.1% used artificial tears, 49% ophthalmic gel, 22.7%, oral moisturiser 18.5% pilocarpine. 62.8% of patients received immu-

Table I. Socio-demographic characteristics.

Socio-demographic characteristics.	n. patients: 252
Age in years (mean ± SD)	52.6 ± 14.8
Gender (% female)	98.4
Time of evolution of the disease in years (mean ± SD)	7.3 ± 7.5
Centre of attention (%)	
• Public	57.1
• Private	42.9
Scholarship (%)	
• Incomplete primary	11.3
• Complete primary	15.6
• Incomplete secondary	16.4
• Complete secondary	21.4
• Incomplete tertiary	5.9
• Full tertiary	9.7
• Incomplete college	5
• Full university	14.7
Occupation (%)	
• Unemployed	5.5
• Professional	13.1
• Student	1.3
• Teacher	6.4
• Merchant	5.5
• Administrative employee	9.7
• Housewife	39.8
• Craft	9.3
• Others / retirees	9.3

SD: standard deviation.

Table II. Results of the VAS.

VAS (0-100mm)	mean ± DE
Xerophthalmia	56.9 ± 30.3
Xerostomia	56.7 ± 31
Xeroderma	52 ± 31.5
Xerovagina	43.1 ± 35.9
Fatigue	48.9 ± 33.3

VAS: visual analogue scales.

nomodulatory treatment with hydroxychloroquine and 17.2% treatment with immunosuppressive drugs.

Confounding variables

The frequency of osteoarthritis and fibromyalgia was 36.3% and 21.4%, respectively. The mean score of depression evaluated by PHQ-9 was 8.9 (±6.5). The mean score of anxiety was 7.8 (±5.9). With regard to physical activity, tobacco, alcohol consumption, and arterial hypertension, these results are summarised in Table III.

Work productivity and ADL impairment

The most affected WPAI's domain

was impairment on ADL due to health: 34.17 % [±30.94 (95% CI: 30.35–37.99)]. The results are summarised in Table IV.

Because the entire study population was represented in impairment on ADL due to health domain, this variable was considered the most appropriate to evaluate association with different manifestations of the disease. In the bivariate analysis, the variables found to be significantly associated with deterioration in ADL due to health were: unemployment, xerophthalmia, xerostomia, xeroderma, xerovagina, fatigue, arthralgia, arthritis, myalgia, Raynaud's phenomenon, polyneuropathy, cutaneous vasculitis, fibromyalgia, depression and anxiety (Table V).

The variables that showed a significant and independent association in the robust regression multivariate analysis were: xerostomia, arthritis, and depression; they are described in Table VI.

The mean of deterioration in ADL due to health was 38.2 (±30.7) in patients treated in public centres *versus* 28 (±30.6) in those who were treated in private sites, being this difference statistically significant. No statistically significant differences were found in the latter, between patients with complete secondary education or higher [33% (±31)] *versus* patients with lower educational level [35.7% (±31.1)].

Considering the differences found in the patients treated in the private *versus* public centres, a model linear regression was performed to each group of patients, considering the impairment on ADL due to health as the dependent variable. In public centres, the robust multivariate regression analysis showed an independent and statistically significant association of deterioration in ADL with the variables of xerostomia [coefficient β: 0.30 (95% CI: 0.1–0.5)], moderate depression [β coefficient: 27.2 (95% CI: 13.5–40.8)], moderately severe depression [β coefficient: 37.7 (95% CI: 25–50.3)] and severe depression [β coefficient: 30.9 (95% CI: 10.5–51.1)].

Regarding private centres, the robust multivariate regression analysis showed an independent and statistically significant association with the vari-

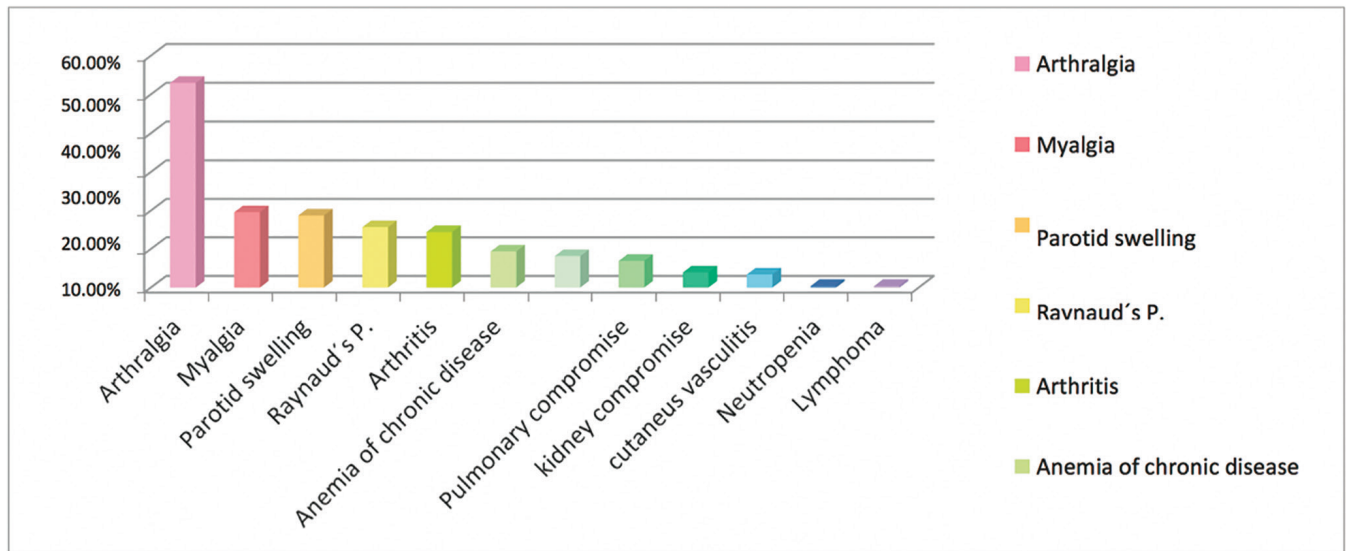


Fig. 1. Frequency (%) of systemic clinical manifestations within the previous 4 weeks.

Table III. Description of other independent variables (possible confounders).

Variables	n. patients: 252
Osteoarthritis (%)	36.3
Fibromyalgia (%)	21.4
Depression (mean ± SD PHQ9 score)	8.9 ± 6.6
Anxiety (mean ± SD GAD7 score)	7.8 ± 5.9
Physical activity: IPAQ score ((METs-minutes/week. (Median, IQR))	1113 (297-2376)
Tobacco (WHO STEPS)	
- Current consumption (%)	8.4
- Daily consumption (% of patients with current consumption)	76.2
- Daily consumption time in years (mean ± SD)	14.4 ± 9.7
- Cigarettes/day (mean ± SD)	5.1 ± 5.4
- Others/day (mean ± SD)	0
- Past consumption (%)	24.6
- Time you stopped smoking in years (mean ± SD)	14.4 ± 10.9
Alcohol (WHO STEPS)	
- Consumption in the last 12 months (%)	48.9
. Daily (%)	7.1
. 5-6 days/week (%)	0.9
. 1-4 days/week (%)	18.6
. 1-3 days/month (%)	42.5
. Less than once a month (%)	30.9
- Average number of glasses/day when drinking alcohol (mean ± SD)	1.4 ± 1.1
- Maximum number of glasses on the same occasion in the last 12 months	1.9 ± 1.4
Hypertension (WHO STEPS)	
- Diagnosed last year by health professional (%)	22.8
- Treatment or advice for AHT:	
. Medication last 2 weeks (%)	24.4
. Special diet prescribed by a doctor (%)	23
. Advice or treatment to lose weight (%)	22.7
. Advice or treatment to stop smoking (%)	4.9
. Advice for exercising (%)	40.4
. Visits to healers for hypertension (%)	0.4
- Traditional or herbal medication for hypertension (%)	4.3

SD: standard deviation; IQR: interquartile range.

ables of xerostomia [coefficient β : 0.3 (CI 95%: 0.1–0.4)], use of oral moisturiser [coefficient β : -14.5 (95% CI: -3.5 to -14.2)], moderate depression [β

coefficient: 19.8 (95% CI: 0.3–39.4)], moderately severe [β coefficient: 37.2 (95% CI: 18.6–56)] and severe [β coefficient: 41.3 (95% CI: 18.8–63.8)].

Discussion

The immune dysregulation present in rheumatological diseases leads to systemic inflammation, organ damage, and a variety of physical and neurocognitive manifestations that can reduce functionality, health-related quality of life, and performance in paid and unpaid work (8).

Published studies suggest that up to 37% of patients with scleroderma (22) and 54% of patients with SLE (23) are unemployed. Likewise, patients who are employed may experience significant limitations that reduce their productivity in the workplace (24).

Despite the fact that pSS is a common disorder that affects patients physically, mentally and socially, the impact of this pathology on work productivity and ADL has not been evaluated in Argentina, and few studies have evaluated work productivity in patients with pSS in other countries.

In this study carried out on patients with pSS, it was found that the most affected domain of WPAI corresponded to the deterioration in ADLs due to health. It should be noted that the latter was the only domain that was representative of the entire population included in this study, given the high percentage of patients without a remunerated job (particularly housewives) at the time of the evaluation. The restriction of applicability of the WPAI GH in only employed patients, has been recognised

Table IV. Results of work productivity and ADL impairment.

Work productivity	mean ± SD	95% CI
Work time lost due to health (%)	15.7 ± 30.1	9.6-21.9
Disability during work due to health (%)	27.2 ± 30.7	21.2-33.1
% total work disability due to health	33.7 ± 35.8	26.4-41.
Impairment on ADL due to health (%)	34.2 ± 30.9	30.6-38

SD: standard deviation.

Table V. Impairment on ADL due to health. Bivariate analysis.

Impairment on ADL due to health	B coefficient	95% CI	p-value
Age	0.1	-0.2 to 0.4	0.4
Sex	22.1	-8.5 to 52.7	0.2
Time of disease duration	0.3	-0.3 to 0.8	0.3
Activity			
Housewife (ref. Category)	34.3	28 to 40.5	0
Professional	-8.4	-20.7 to 4.1	0.2
Teacher	1.1	-15.7 to 17.9	0.9
Merchant	-7.3	-25.2 to 10.5	0.4
Administrative employee	0.5	-13.5 to 14.6	0.9
Craft	1.2	-13.1 to 15.5	0.9
Unemployed	28.1	10.9 to 45.9	<0.01
Others / retirees / students	-3.1	-16.6 to 10.5	0.7
Xerophthalmia	0.4	0.2 to 0.5	<0.01
Xerostomia	0.4	0.3 to 0.5	<0.01
Xeroderma	0.4	0.2 to 0.5	<0.01
Xerovagina	0.2	0.1 to 0.3	<0.01
Fatigue	0.4	0.3 to 0.5	<0.01
Parotid enlargement	3.6	-6.7 to 13	0.50
Arthralgia	14.5	6.7 to 22.3	<0.01
Arthritis	19.7	7.2 to 32.3	<0.01
Myalgia	15.4	4.9 to 25.8	<0.01
Raynaud's phenomenon	13.9	2.3 to 25.5	0.02
Polyneuropathy	19.5	4.5 to 34.5	0.01
Cutaneous vasculitis.	29.3	4.5 to 54.1	0.02
Lung involvement	-2.8	-18.6 to 12.9	0.7
Kidney involvement	-11.7	-32.3 to 8.9	0.3
Anaemia	8.7	-4.9 to 22.3	0.2
Neutropenia	6.7	-53.9 to 67.3	0.8
Lymphoma	-33.6	-94.2 to 27	0.3
Fibromyalgia	22.5	13.3 to 31.7	<0.01
Osteoarthritis	4.8	-3.5 to 13	0.3
Smoking	-2.5	-11.1 to 6.1	0.6
Hypertension	7.4	-0.6 to 15.3	0.07
Tears art.	1.7	-10 to 13.3	0.8
Ophthalmic gel	6.7	-0.9 to 14.3	0.08
Oral moisturiser	8.1	-1.2 to 17.4	0.09
Secretagogues	-1.6	-11.8 to 8.7	0.8
Hydroxychloroquine	0.02	-8.1 to 8.8	1.00
Immunosuppressants	3.1	-7.4 to 13.6	0.6
Depression			
Absence	13.7	8.1 to 19.3	<0.01
Mild	13.1	4.6 to 21.7	<0.01
Moderate	34.3	25.3 to 43.3	<0.01
Moderate/severe	46.9	36.9 to 56.9	<0.01
Severe	46.9	33.9 to 59.9	<0.01
Anxiety			
Absence	16.8	10.9 to 22.6	<0.01
Mild	17.7	9.01 to 26.4	<0.01
Moderate	32	22.4 to 41.7	<0.01
Severe	35.7	24.9 to 46.5	<0.01
Physical activity	-0.00006	-0.00018 to 0.00007	0.38

as a limitation of this instrument (25). However, the WPAI questionnaire has been widely validated in numerous rheumatic diseases; for this reason, it is considered a solid tool to evaluate work productivity and ADL impairment. Patients with pSS complain of a reduced quality of life as result of systemic chronic symptoms, like fatigue, depression and anxiety (26).

The variables of xerostomia, arthritis, and depression were found to be independently associated with deterioration in ADLs due to health. This is consistent with other studies, which have identified depression as a predictor of occupational disability in these individuals (5, 6).

A possible explanation to this is related to IL-1 β signalling. It has been hypothesised that IL-1 β in the brain possibly represents a final common pathway for fatigue, and has also been implicated in depression, thus explaining why fatigue and depression are so tightly associated (26).

Likewise, as reported by Baldini *et al.*, the presence of arthritis was reported as a determinant of deterioration in ADL due to health, and a higher percentage of absenteeism was observed in this group of patients (27).

A study carried out in a German cohort of patients with pSS showed that the disease has a high impact on work productivity, due the fact that only half of patients in economically productive age remain active in the workforce (5). When comparing women with pSS with healthy controls, it was found that these patients had stopped working at younger age, and had a higher level of sick leave (5). An investigation by Meijer *et al.* in Dutch population, reported that patients with SSp had a higher percentage of unemployment, worked fewer hours on average, and had a lower frequency of full-time jobs, compared to healthy controls. It should be noted that the aforementioned study did not use a validated questionnaire such as the WPAI GH; a questionnaire specifically designed for that study was used instead (7). As published by Bowman *et al.*, higher unemployment and lower compliance with work hours were observed in patients with pSS, compared to controls. It should be clarified that in

Table VI. Impairment on ADL due to Health. Multivariate analysis (robust regression)

Impairment on ADL due to health	β coefficient	95% CI	p value
Xerostomia	0.3	0.1 to 0.4	<0.01
Arthritis	11.2	0.6 to 21.7	0.04
Depression			
Mild/moderate	8.8	1.4 to 16.1	0.02
Severe/moderate	25.5	13.8 to 37.1	<0.01
Severe	36.9	26.9 to 46.9	<0.01
	32.2	16.3 to 48.1	<0.01

Adjusted R: 0.40.

this work the Stanford Health Evaluation questionnaire was used, implementing a modified version of the component that evaluates elements related to the economy to measure the loss of work productivity (28).

Regarding our country, there are few publications on work productivity in other autoimmune rheumatic diseases. A study carried out by Bru Morón *et al.* included the Argentine population with rheumatoid arthritis and reported a mean absenteeism from work of 14%, with an average of 6.3 (± 12.6) hours lost working per week. Likewise, a mean decrease in work performance or presenteeism of 38.4% (± 26) was observed, with a total productivity loss of 45% (± 30) (14).

On the other hand, in our work we found that patients treated in public centres obtained worse scores in impairment of the ADL domain due to health, this difference being statistically significant compared to private centres. The greater deterioration of ADLs due to health in patients from public centres observed in our analysis could be an expression of the impact that the socioeconomic condition would have at this level. Initially, the monthly income variable was considered as the best approximation of the socioeconomic condition, however, changes in the country's economy and the time elapsed for the inclusion of patients determined that it was not adequate for analysis at the end of this study. For this reason, the variables of educational level and site of care were considered as surrogates of the socioeconomic condition. It should be noted that Argentina's health system is fragmented, including social security (for example, income-related contributions from employers and employees),

the private sector, and the public sector; for this reason, it is considered as an approximation to the socioeconomic condition.

Within the limitations of this work, we can mention the lack of control group. However, when designing the protocol, it was considered unlikely to find people of the same sex and similar age group without another pathology that could affect work productivity and who present similar living conditions. Another limitation is the possibility of selection bias, since the project was carried out in Rheumatology reference centres, so the patients included were probably more controlled subjects with a greater awareness of their disease. This factor could also make the sample less representative of the general population of patients diagnosed with pSS, potentially affecting its external validity. On the other hand, several systemic manifestations of the disease are relatively infrequent, particularly if we seek to detect their presence in the same period of time considered by the WPAI questionnaire. For this reason, there could be associations not found in this study. It should be noted that scales assessing disease activity or damage were not included; ESSPRI index (EULAR Sjögren's Syndrome Patient Reported Index) (29), ESSDAI (EULAR Sjögren's Syndrome Disease Activity Index) (30) and Sjögren's Syndrome Disease Damage Index (SSDDI) (31). At the time the patients were enrolled in this study, these indexes were only recently available and not widely validated, so their use was not generalised in clinical practice; also, the ESSDAI transcultural adaptation was not available.

It is noteworthy that our study used a questionnaire that, although generic,

was specifically designed and validated to measure the loss of work productivity. Although this tool does not have cut-off points, we observe a compromise in work productivity in all domains evaluated.

The data found are a further contribution to the knowledge about the negative impact of pSS on work productivity and ADL. They intend to contribute to a better understanding of the disease, considering all the aspects involved, therefore a multidisciplinary approach of health care team and the development of new therapeutic alternatives result in better opportunities and work productivity of this patient population.

Conclusion

We found a compromise in all the WPAI domains. The variables of xerostomia, arthritis, and depression were found to be significantly and independently associated with deterioration of ADL. The greater impairment of ADL due to health observed in patients treated in public centres could express the negative impact of socioeconomic condition on work productivity and ADL. Knowledge of these aspects should be considered by health care providers for a better management of patients suffering from this disease.

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