Patient-reported experience and health-related quality of life in patients with primary Sjögren's syndrome in Europe

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ABSTRACT

Objective. *The study aims to provide novel findings on geographic variation in the management of primary Sjögren's syndrome (pSS) in Europe, an underdiagnosed, long-term autoimmune disease.*

Methods. *Starting from the lack of comparable information on patients' experience, quality and efficiency of care delivered to pSS patients in Europe, the approach is to collect and analyse patients reported data from an international survey. To assess and compare access and quality of care to pSS along their care-path we developed and validated a questionnaire administered to a large cohort of pSS patients in selected European countries. Regression models have been applied to survey data to compare quality and volumes of care across Europe.*

Results. *Both follow-up and number of visits with a specialist of the patient are influenced by the severity of the disease with differences among countries. The results show some extent of variations in access and treatments delivered to pSS patients and also their perceived quality of life and satisfaction for SS care in Europe.*

Conclusion. *Findings contribute to support healthcare professionals' decision making and the organisation of care delivery by taking into consideration the patients' point of view and preferences.*

Introduction

Geographic variation in spending, utilisation and quality of care, across and within countries, is well documented. Part of this geographic variation is due to differences in population health needs and preferences. However, some of the variation may be unwarranted and driven by other factors, including professional discretion, the availability and distribution of resources, differences in the organisation or delivery of care and in payment models (1). International and national comparative research allows to approach unwarranted variations, to identify best practices and, create significant value in health care (2). Data benchmarking also contributes to engage the multispecialty professionals, *e.g.* specialists and general practitioners (GPs), involved in the care of cohort of patients and holding them accountable for the patients that they have in common. This is particularly true for patients with long term chronic diseases who are likely to receive suboptimal care with large variations in the provision of evidence-based treatments and services and gaps in the disease management due to fragmentation of care and poor coordination among the different care settings (3, 4).

Sjögren's syndrome (SS) can occur alone, primary SS (pSS), or in association with other specific systemic autoimmune rheumatic diseases (5). It is a heterogeneous, underdiagnosed, complex systemic autoimmune disorder typically characterised by salivary and lacrimal inflammation and dysfunction (6). During the disease course, several organs and systems may be involved (7-9) and, in a minority of cases, lymphoproliferative complications may also occur (10).

Several studies on the epidemiology of autoimmune diseases performed within the past several decades revealed a prevalence of SS between 0.3% and 4.83% according to the population investigated (11). Recent studies revealed a lower prevalence between 0.031% to 0.049% (12-14). The exact prevalence of SS is unknown due to the heterogeneity of the populations and geographic areas studied, the utilisation of different diagnostic tests or the number of different classification criteria proposed over the time.

Such a low prevalence chronic syndrome may have an insidious onset and a variable course with a broad spec-

trum of clinical manifestations, so the diagnosis may be delayed, or SS patients may be missed and misclassified as other rheumatic disease.

This is frequent in cases of non-common and rare diseases and generates high costs for the health care system because of years of wrong diagnostic tests and treatments, eventually expensive, that hamper the health-related quality of life (HRQoL) of patients (15, 16). So, it is relevant to the literature, which usually addresses high-prevalence chronic diseases.

In general, pSS does not impair life expectancy and is considered as a benign disease, but the impact of the disease is not negligible, imposing a considerable burden on patients' lives (17-19). In fact, despite clinical practice guidelines on diagnosis and management of SS have been published, some unmet needs for pSS are still to be addressed (20). Misdiagnosis is still common and the mean length of time between the onset of symptoms and diagnosis is about 7 years, biomarkers of disease severity and outcome are uncertain (21) and pSS patients are likely to experience worse quality of life, use more care services and report higher out of pocket expenses compared to controls (18, 22-26). The main factors contributing to suboptimal levels of care and treatments include the lack of awareness and knowledge of the disease among the healthcare professionals encountered by pSS patients, gaps in evidence-based therapeutic and clinical guidelines for the management of pSS (27, 28). All these factors contribute to a situation of lack of clear and homogenous medical guidelines for the management of patients both:

- in primary care, since the insurgence of symptoms with consequent delays in the diagnosis as in rare rheumatologic diseases (29);
- in specialist care, responsible for the diagnosis process and the recommendations for the follow-up and the take in charge of the patient.

Consequently, unwarranted variations in clinical and patient-reported outcomes, volumes and costs, are expected, similarly to other rare health conditions (30).

To the best of our knowledge, the currently available evidence on variations in the care to pSS is scarce and of limited generalisability in the different European countries. The present study investigates geographic variations in volumes, reported quality of care and HRQoL and the potential determinants of these variations in Europe.

The analysis will contribute to providing suggestions for a better management of pSS patients by the various professionals enhancing patients' HRQoL and a responsible and efficient utilisation of resources with the ultimate goal to shift to value-based healthcare.

Methods

This work has been carried out within HarmonicSS, a European funded project aiming to gather and combine a large amount of information on pSS in structured data, including large cohorts, that allow more sophisticated statistical studies. It was designed to address gaps in the pSS literature and in particular the lack of references to best practices and guidelines for improving paths of diagnosis and treatment of pSS patients.

Starting from the existing literature, with the collaboration of the clinical partners of HarmonicSS, we designed a survey to collect pSS patients' reported outcomes and experience in Europe.

The survey was firstly designed in Italian language and validated through a pilot survey on a group of patients of selected Italian rheumatologic units. Next, the questionnaire has been revised and translated into several European languages by clinical professionals involved in HarmonicSS and by the European association of pSS patients.

The survey was administered to pSS patients diagnosed before 2017, to collect information on other dimensions regarding their experience with follow-up care, in particular type and volumes of routine tests and medical examinations, access to emergency care, organisation of the centre, drugs prescriptions and financial burden due to the disease and their reported quality of life as well as socio-demographic data.

Participation in the survey was anonymous and on a voluntary basis according to the GDPR.

Survey

The survey was administered between January 2019 and March 2020 by clinical partners of HarmonicSS to pSS patients at their clinical centres in the following countries: Italy, Germany, France, Sweden, Norway and United Kingdom in paper format. A paper questionnaire, in the language of the country of residence, was administered to each patient entering the clinical centre from January to March.

Additionally, the same questionnaire was administered to pSS patients via web through the National and European associations. pSS patients received a link to the digital survey available online in eight European languages (Dutch, English, Greek, German, French, Italian, Spanish, Swedish) through their emails.

The survey consists of 43 questions and 124 items, the whole questionnaire is available upon request to the authors. It explores several dimensions of patients' life with pSS on a sample of patients from several European countries. Patients' socio-demographic information are also collected.

A section of the survey explores the frequency, with a Likert-type scale ranging from "never" up to "every three months" of treatment and follow-up management of the patients focusing on follow-up exams and visits. (9 questions and 43 items).

A further section of the survey collects data on the experience regarding the specialist centre in which the patient is treated, including quality of the information received and the centre organisation that summarises the aspects: coordination among professionals, level of assistance and organisation, with a Likert-type scale. Additionally, information on number of yearly emergency accesses and hospitalisation are collected. (11 questions and 16 items).

A set of items using a binary yes/no response format with the possibility of specifying drugs' names is adopted to get the pharmacological therapy of the patient. A wide range of quality-of-life aspects with pSS: feelings; financial burden; dexterity; job and leisure activities; social relationships; mobility; cognition; ability to conversate; vision

ability and pain are carefully investigated through Likert-type scales. (8 questions and 51 items) (26).

Key variables

Follow-up care received by patients in each country is analysed through five items of the questionnaire, which ask the frequency of different types of exam in the latest 12 months: rheumatologic examinations; haemato-chemical tests; ultrasounds; computerised tomographic examinations; endoscopic checks.

The variable "follow-up" is built from the five items: first, we converted the frequency of exams in the number of exams in the latest year to obtain a measure of total number of follow-up examinations. Same procedure was applied to the variable regarding the frequency of visits for each specialty in the latest year.

With regard to the outcome measures, the dummy variable related to the patient-reported clinical outcomes "Complication of pSS", summarises the information of experiencing at least an episode of complication of pSS, that is, either having at least one emergency access to or a hospitalisation in a healthcare facility because of pSS during the previous 12 months. Moreover, the survey provides several items regarding a range of aspects of the HRQoL of the patient. We used the items in the questionnaire to compute the health utility index (HUI) mark 3 recurring to some reasonable conversions of our items into HUI mark 3 multivariate values (31).

Neurological involvement is quite uncommon in pSS, with central nervous system manifestations being reported in less than 5% of patients (32). Therefore, our first assumption is that the disease does not totally impair any physical or mental ability. So, we exclude the possibility of the minimum level of utility for vision, speech, ambulation, dexterity, cognition. In absence of any contrary evidence in the literature, we assume that pSS does not affect hearing. We allow all the possible levels of utility for emotion.

Then, we consider the item "ability to find a word during conversation" for the speech dimension; we consider the items regarding modification of the living spaces and walking to assess the level of utility regarding ambulation. Since we have the item on walking ability for only 25% of the observations, we chose to assign a level two of utility to those who reported adaptations of the living space or walking difficulties. It is a conservative approach to avoid including artificial variation in the data.

For the aspect of dexterity we considered the item "performing daily activities like cooking dressing cleaning".

The cognition dimension is assessed using a set of three items regarding memory and concentration. The utility of the sphere of emotion, which is the most affected by the disease, is evaluated with a set of eight items concerning mood and the emotional attitude towards the life with pSS.

We also considered dummies variables for:

1. medical consultation with a GP in the previous 12 months (GP visit);
2. quarterly visits with an ophthalmologist (quarterly ophthalmologist);
3. rheumatological comorbidities (sSS) identifies patients with at least one further rheumatological clinical condition.

Each one of four medical groups that are structured on the base of the complexity of the pharmacologic therapy of the patient. Medical group 1 includes all the patients who take nothing or just artificial tears and/or saliva and/or NSAIDs; medical group 2 comprehends patients who take Plaquenil and eventually corticosteroids in addition to group 1's therapy; medical group 3 includes patients who take immunosuppressants different from Plaquenil; medical group 4 contains all the patients with other therapies, residually.

The items on sociodemographic include gender (male, other gender), age, level of education (organised in two alternative dummies: university, high school or university), marital status (Partnership identifies patients who are either married or live with a partner), self-rated health and country of residence. In our analysis we also took into account whether the survey was administered at the clinical centre or online.

Analytical strategy

We estimated four regression models. Two count models are chosen for the two discrete variables "Follow-up" and "Visits with a specialist" to analyse the determinants of access to visits and treatments. According to the result of the over-dispersion test (33) we adopted respectively a Poisson and a negative binomial modelling to take into account the behaviour of the variance of the distribution in the two variables. The opportunity of using parametric models for summed scores of the Likert scale has been widely addressed in the literature (34-36).

The determinants of reported outcome were analysed by considering as dependent variables both the reported clinical outcomes, through a logit regression and HUI trough a linear regression model. All the regression models control for socio-demographic, dummies for countries and medical groups. Robust standard errors are adopted to handle a mild heterogeneity in the residuals.

The data were analysed using STATA/IC 15.1 software.

Results

395 questionnaires from patients diagnosed before 2017 were collected. The main characteristics of the cohort are summarised in Table I.

Geographic variation in SS patients' follow-up

The multiple group comparison tests show significant geographic variation across countries for all the outcome variables examined.

Roughly the average follow-up is made up of rheumatologic exams for one third, one third blood exams and one third diagnostic exams which give information on disease specific systemic involvement and comorbidities. The European countries studied are quite homogenous concerning the composition of follow-up care for pSS patients. Then the focus of our analysis is the volume variability of periodic exams had by patients (third column of Table II). The measure ranges from 1.8 in Sweden to 6.66 in Germany and it is described by a High-Low ratio of 3.7.

Table I. Descriptive statistics of the sample.

Country	Number of respondents	Female percentage	Mean age (std dev)
France	39	94.6%	61.46 (1.78)
Germany	32	96.2%	56.59 (2.67)
Italy	105	93.3%	59.68 (1.16)
Norway	32	93.7%	66.44 (1.63)
Spain	68	95.5%	49.03 (1.24)
Sweden	54	92.6%	65.02 (1.79)
United Kingdom	65	90.5%	57.37 (1.58)
All	395	93.5%	58.70 (0.66)

Table II. Average volume of special visits and follow-up exams, percentage of patients experiencing acute episodes and HUI by country.

Country	Mean number of visits with a specialist (std dev)	Mean number of follow-up exams (std dev)	% of patients who had acute episode	HUI (std dev)
France	9.15 (1.02)	5.09 (0.66)	23.08%	0.52 (0.052)
Germany	8.91 (1.12)	6.66 (0.39)	9.38%	0.70 (0.064)
Italy	8.12 (0.49)	6.15 (0.29)	9.52%	0.61 (0.034)
Norway	3.84 (0.67)	2.97 (0.36)	15.63%	0.62 (0.047)
Spain	11.15 (0.87)	5.38 (0.30)	38.24%	0.60 (0.033)
Sweden	3.56 (0.45)	1.8 (0.27)	3.70%	0.72 (0.034)
United Kingdom	5.78 (0.5)	3.61 (0.33)	15.38%	0.46 (0.047)
All	7.45 (0.29)	4.70 (0.16)	16.46%	0.59 (0.017)
Multiple group comparison test	$p<0.001$	$p<0.001$	$p<0.001$	$p<0.001$

Table III. Follow-up analysis.

Dependent variable: follow-up			
Independent variable	IRR Coefficient	Std. Err.	Confidence Interval
Med group2 (ref med group1)	1.120*	0.076	(0.980; 1.280)
Med group3 (ref med group1)	1.415***	0.117	(1.203; 1.663)
Med group4 (ref med group1)	1.238***	0.093	(1.069; 1.434)
France (ref Average)	1.096	0.106	(0.906; 1.325)
Germany (ref Average)	1.200**	0.109	(1.005; 1.433)
Italy (ref Average)	1.416***	0.081	(1.266; 1.584)
Norway (ref Average)	0.775**	0.082	(0.630; 0.953)
Spain (ref Average)	1.361**	0.187	(1.039; 1.783)
Sweden (ref Average)	0.477***	0.051	(0.386; 0.588)
UK (ref Average)	1.029	0.084	(0.878; 1.207)
Web (ref paper)	0.795	0.126	(0.583; 1.083)
Complication of pSS	1.093	0.077	(0.953; 1.255)
Male (ref female)	1.128	0.119	(0.918; 1.387)
Other gender (ref female)	1.372	0.719	(0.491; 3.832)
High School or University (ref Middle school or lower)	0.863**	0.053	(0.765; 0.972)
Age	0.998	0.002	(0.994; 1.003)
sSS (ref pSS)	0.909	0.144	(0.667; 1.239)
Self-rated good health (ref bad)	0.993	0.055	(0.890; 1.107)
Visits with a specialist	1.033***	0.005	(1.024; 1.042)
Constant	3.550***	0.687	(2.430; 5.186)

Observations 314. ***$p<0.01$; **$p<0.05$; *$p<0.1$; Pearson goodness of fit test. $p>0.10$.
Notes: medical groups are structured on the base of the complexity of the pharmacologic therapy.

The fourth column of Table II describes the variable "Complications of pSS" and shows that Spain is the country where the largest share of patients experience complication of pSS, on the other side Sweden reports that less than 4% of patients had such an event. The chi-square test performed on this variable shows significant differences across countries ($p<0.001$).

The fifth column of Table II describes the mean and, in parenthesis, the standard deviation of the distribution of HUI across the different countries. The lowest value is scored by UK and, on the opposite, the highest one is reached in Sweden. The Anova test performed on this variable shows significant differences across countries ($p<0.001$).

The estimates of the regression of the dependent variable "follow-up" are reported in Table III.

Follow-up care is more extensive for male; patients with a level of education higher or equal to high school diploma performs less follow-up exams.

As expected, the group of patients who take immunosuppressants different from hydroxychloroquine have a more extensive follow-up, as those in the residual group 4. The former includes patients whose pharmacologic therapy is stronger due to a greater severity of the disease.

The number of visits with a specialist is correlated with the number of follow-up exams. This might be either for a major need of the patient or a larger demand induced by the offer. The variability is expected and important to the study since we face a health condition for which strict guidelines and standards do not exist.

Our model aims to explain such differences in the volumes and, although we found some noteworthy relations, these factors are not able to explain all the variations.

Visits with rheumatologists are the most common. Also visits with dentists and ophthalmologists represent an important share but they likely include periodic visits not necessarily related with pSS other than recommended periodic follow-up visits. The remaining panorama of the specialists consulted by patients is very heterogeneous in line with the characteristic of the disease being a systemic autoimmune disorder.

The estimates for the regression of the dependent variable "Visits with a specialist" are reported in Table IV.

The analysis suggests new perspectives of the demand of health care services for pSS.

The number of follow-up exams is positively correlated with the number of visits with a specialist, according with the previous result.

GP visit positively affects the number of visits with a specialist. Education, gender and medical group seem to not sig-

Table IV. Regression of visits with a specialist.

Dependent variable: Visits with a specialist			
Independent variable	IRR Coefficient	Std. Err.	Confidence Interval
Med group2 (ref med group1)	1.021	0.090	(0.859; 1.213)
Med group3 (ref med group1)	1.192	0.140	(0.947; 1.500)
Med group4 (ref med group1)	0.995	0.098	(0.820; 1.207)
France (ref Average)	1.148	0.140	(0.904; 1.459)
Germany (ref Average)	1.180	0.150	(0.919; 1.515)
Italy (ref Average)	1.130	0.090	(0.966; 1.322)
Norway (ref Average)	0.715***	0.090	(0.558; 0.915)
Spain (ref Average)	1.298	0.213	(0.941; 1.791)
Sweden (ref Average)	0.776**	0.088	(0.621; 0.970)
UK (ref Average)	0.880	0.089	(0.721; 1.072)
Web (ref paper)	1.282	0.245	(0.882; 1.865)
Complications of pSS	1.124	0.106	(0.934; 1.353)
Male (ref female)	0.808	0.118	(0.607; 1.075)
Other gender (ref female)	0.684	0.455	(0.186; 2.520)
University (ref High School or lower)	1.107	0.080	(0.925; 1.241)
Age	1.004	0.003	(0.998; 1.010)
sSS (ref pSS)	1.033	0.190	(0.720; 1.483)
Self-rated good health (ref bad)	1.021	0.076	(0.883; 1.181)
GP visit (ref no GP visit)	1.258**	0.129	(1.029; 1.538)
Follow-up	1.095***	0.014	(1.068; 1.123)
lnalpha	-1.577***	0.135	(-1.841; -1.314)
Constant	2.967***	0.721	(1.843; 4.776)

Observations 304. ***p<0.01; **p<0.05; *p<0.1.
Notes: medical groups are structured on the base of the complexity of the pharmacologic therapy.

Table V. Regression of episode of complication of pSS.

Dependent variable: Complication of pSS			
Independent variable	OR coefficient	Std. Err.	Confidence interval
Med group2 (ref med group1)	1.046	0.496	(0.413; 2.649)
Med group3 (ref med group1)	5.573***	3.063	(1.898; 16.366)
Med group4 (ref med group1)	1.849	0.941	(0.682; 5.013)
France (ref Average)	1.384	0.801	(0.444; 4.308)
Germany (ref Average)	1.058	0.741	(0.268; 4.179)
Italy (ref Average)	1.166	0.528	(0.479; 2.834)
Norway (ref Average)	2.525	1.459	(0.814; 7.838)
Spain (ref Average)	0.510	0.363	(0.126; 2.056)
Sweden (ref Average)	1.228	0.913	(0.286; 5.271)
UK (ref Average)	0.472	0.241	(0.173; 1.284)
Web (ref paper)	13.607***	11.871	(2.46; 75.223)
Male (ref female)	10.459***	6.642	(3.013; 36.308)
University (ref High School or lower)	1.034	0.387	(0.497; 2.155)
Age	0.968**	0.016	(0.936; 1)
Self-rated good health (ref bad)	0.294***	0.114	(0.138; 0.628)
sSS (ref pSS)	2.720	2.124	(0.589; 12.570)
GP visit (ref no GP visit)	4.022*	3.284	(0.812; 19.926)
Constant	0.007***	0.008	(0.001; 0.072)

Observations 316. ***p<0.01; **p<0.05; *p<0.1.
Notes: medical groups are structured on the basis of the complexity of the pharmacologic therapy.

nificantly affect the dependent variable. Norway is characterised by a significant and lower probability than the average of taking a number of visits with a specialist with respect to the average.

Geographic variation in SS patients' accessing emergency departments

The analysis of the dependent variable "Complication of pSS" is reported in Table V.

The results show that the probability of accessing the emergency department for pSS reasons is higher for male patients than for female counterparts. The effect in this case could be even stronger since pSS usually has a more severe clinical manifestation in men (37, 38), although typically affects women (39). With regard to the variable self-rated good health, which controls for unobservable confounding related to individual wellbeing, patients who report good health are likely to use the emergency department with a lower probability than those who report bad health. Patients who follow a pharmacological therapy including immunosuppressants different from Plaquenil have a higher probability of the event. This is because of the severity of the disease and eventual possible complications derived by the use of more aggressive treatments (*i.e.* infectious risk), (40).

Age slightly reduces the probability of an acute event. It is likely that older patients have more experience of the health services and make less inappropriate use of emergency care (41-45).

Geographic variation in SS patients' perceived quality of life and satisfaction

The survey provided us with several items regarding a range of aspects of the HRQoL of the patient. Coherently with the existing literature, the impact of pSS on HRQoL is significant (18, 26, 46-48). The literature documents that the functional disability and the HRQoL of pSS patients is similar to patients with rheumatoid arthritis, systemic lupus erythematosus and fibromyalgia (49-51).

The estimates of the regression of the HUI are reported in Table VI.

The HRQoL of the patient is found to increase with age. This effect might be interpreted as a relative lower impact of the disease on HRQoL for old-aged people who typically are likely to be affected by a range of chronic diseases than young people for whom pSS could be the unique relevant clinical condition.

Performing ophthalmologic visits every three months is positive correlated with the HRQoL. We suppose that this practice is positive for the patients, indeed ocular dryness is one of the major problems of the pSS. However, the variable could also capture the eventual unobserved effect of income on the HRQoL, for those countries in which patients sustain the cost of ophthalmologic visits, especially Germany and UK. Even in these countries, the varia-

Table VI. Regression of health-related quality of life analysis.

Dependent variable: HUI			
Independent variable	Coefficient	Std. Err.	Confidence interval
Med group 2 (ref med group 1)	.007	.034	(-0.060; 0.074)
Med group 3 (ref med group 1)	.0009	.044	(-0.086; 0.088)
Med group 4 (ref med group 1)	-.086*	.048	(-0.181; 0.009)
France (ref Average)	.0170	.043	(-0.069; 0.103)
Germany (ref Average)	.082*	.043	(-0.003; 0.167)
Italy (ref Average)	-0.012	.031	(-0.073; 0.048)
Norway (ref Average)	-0.016	.037	(-0.090; 0.057)
Spain (ref Average)	0.077	.049	(-0.019; 0.172)
Sweden (ref Average)	-0.045	.033	(-0.110; 0.020)
UK (ref Average)	-0.102*	.039	(-0.178; -0.025)
Web (ref paper)	-0.051	.051	(-0.151; 0.049)
Complication of pSS	-0.023	.038	(-0.098; 0.051)
Male (ref female)	0.080*	.042	(-0.002; 0.162)
Other gender (ref female)	0.166***	.051	(0.065; 0.267)
University (ref High School or lower)	0.068**	.029	(0.011; 0.125)
Age	0.003	.001	(0.001; 0.005)
Self-rated good health (ref bad)	0.330***	.033	(0.266; 0.394)
Living with partner (ref living without partner)	-0.055*	.027	(-0.109; -0.001)
GP visit (ref no GP visits)	-0.079**	.037	(-0.152; -0.006)
Visits with a specialist	-0.008***	.003	(-0.014; -0.003)
Quarterly ophthalmologist (ref no quarterly ophtalmologist)	0.103**	.045	(0.014; 0.191)
Constant	0.576***	.052	(0.474; 0.677)

Observations 270. ***p<0.01; **p<0.05; *p<0.1.
Notes: medical groups are structured on the basis of the complexity of the pharmacologic therapy.

ble describing education should be able to partially capture the eventual latent effect of income.

Both GP and visits with a specialist are likely to be negatively correlated with HRQoL. The main interpretation is that patients with major health needs have a lower HRQoL and at the same time needs many visits (52).

The self-assessed health status explains some variability. "Living with partner" is negative correlated with HRQoL, the reason might be the burden of the disease within familiar relationships and sexual dimension.

We also remark that being in the fourth medical group, which groups patients whose pharmacological therapy is not clear, has a negative impact on HRQoL. Likely, this depends on the lower quality of the treatment. In fact, the literature documents that appropriate drug therapies are effective in relieve the burden of pSS symptoms (53).

Discussion

The results show some extent of variations in access and treatments delivered to pSS patients and also their perceived HRQoL and satisfaction for SS care in Europe.

Both the follow-up and the number of visits with a specialist of the patient are influenced by the information and the severity of the disease according to our classification based on the pharmacologic therapy. The country dummies capture some geographic variation and we can distinguish UK, Norway and Sweden, which seem to provide patients with a less extensive care-management.

The analysis of HUI suggests that frequent visits with the ophthalmologist might improve the HRQoL of the patients. Therefore, as in Norway and Sweden, the access to this kind of service should be facilitated by means of exemptions or specific reimbursement policies for pSS patients.

A further examination of the relations between outcome variables, after controlling for patients' characteristics, suggests both the positive effect of practices with more intensive follow-up on the HRQoL of the patient and the preventive effect of more specialist visits on possible acute events due to pSS.

These findings are valuable for contributing to support healthcare professional decision making and the organisation of care delivery by taking into consideration the patient point of view and preferences.

This work implements an effective approach for exploiting for analysing the care of rare and non-common chronic condition across different countries in Europe, with the aim of providing important insights for the identification of good practices and improvement of the management and the HRQoL of patients as well as a responsible and efficient utilisation of resources (30) both at specialist and primary care level with the ultimate goal to shift to value-based healthcare (54).

Limitations of this work are the nature of the enrolment of pSS patients in the survey which did not allow us to get a random sample and low response rate in some countries.

Further research is recommended to define patient-reported experience measures (PREMs) and HRQoL for non-common and rare conditions, for which clear medical guidelines are not available and the disease manifests with non-specific symptoms. Variations in all the stages of the clinical management of the disease included the diagnosis should be analysed to suggest good practices and address inefficient deviation in volumes and costs. The study of the path to the diagnosis of pSS, as for other conditions characterised by non-specific manifestation, independently of prevalence could suggest indications for improving the process leading to the diagnosis and allow earlier treatment of the disease, especially by increasing awareness among professionals (55). The latter would drive an increase in the HRQoL of patients and a more efficient use of resources (15, 16, 56) to promote value-based healthcare.

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References

1. WENNBERG JE: Time to tackle unwarranted variations in practice. *BMJ* 2011; 342.
2. SEGHIERI C, BERTA P, NUTI S: Geographic variation in inpatient costs for acute myocardial infarction care: insights from Italy.

Health Policy 2019; 123: 449-56.
3. BROEMELING AM, WATSON DE, PREBTANI F: Population patterns of chronic health conditions. co-morbidity and healthcare use in Canada: implications for policy and practice. Healthc Q 2008; 11: 70-6.
4. STUKEL TA, GLAZIER RH, SCHULTZ SE *et al*.: Multispecialty physician networks in Ontario. *Open Med* 2013; 7: e40-55.
5. ALUNNO A: Comment on: Equal rights in autoimmunity: is Sjögren's syndrome ever 'secondary'? *Rheumatology* (Oxford) 2021; 60: e32-e33.
6. DANIELS TE, FOX PC: Salivary and oral components of Sjögren's syndrome. *Rheum Dis Clin North Am* 1992; 18: 572-89.
7. ARGYROPOULOU OD, VALENTINI E, FERRO F *et al*.: One year in review 2018: Sjögren's syndrome. *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S14-26.
8. BALDINI C, FERRO F, LUCIANO N, BOMBARDIERI S, GROSSI E: Artificial neural networks help to identify disease subsets and to predict lymphoma in primary Sjögren's syndrome. *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S137-44.
9. BRITO-ZERÓN P, ACAR-DENIZLI N, NG WF *et al*.: How immunological profile drives clinical phenotype of primary Sjögren's syndrome at diagnosis: analysis of 10.500 patients (Sjögren Big Data Project). *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S102-12.
10. GOULES AV, TZIOUFAS AG: Lymphomagenesis in Sjögren's syndrome: Predictive biomarkers towards precision medicine. *Autoimmun Rev* 2019; 18: 137-43.
11. TOMSIC M, LOGAR D, GRMEK M, PERKOVIC T, KVEDER T: Prevalence of Sjögren's syndrome in Slovenia. *Rheumatology* 1999; 38: 164-70.
12. SARDU C, COCCO E, MEREU A *et al*.: Population based study of 12 autoimmune diseases in Sardinia, Italy: prevalence and comorbidity. *PLoS One* 2012; 7: e32487.
13. Prevalencia de las enfermedades raras: Datos bibliográficos. Informes Periódicos de Orphanet. Serie Enfermedades Raras. Enero 2019. Número 1: Listado por orden alfabético de enfermedades o grupo de enfermedades http://www.orpha.net/orphacom/cahiers/docs/ES/Prevalencia_de_las_enfermedades_raras_por_orden_alfabetico.pdf
14. NARVÁEZ J, SÁNCHEZ-FERNÁNDEZ SÁ, SEOANE-MATO D *et al*.: Prevalence of Sjögren's syndrome in the general adult population in Spain: estimating the proportion of undiagnosed cases. *Sci Rep* 2020; 10. 10627.
15. ANGELIS A, TORDRUP D, KANAVOS P: Socio-economic burden of rare diseases: A systematic review of cost of illness evidence. *Health Policy* 2015; 119: 964-79.
16. LÓPEZ-BASTIDA J, OLIVA-MORENO J, LINERTOVÁ R *et al*.: Social/economic costs and health-related quality of life in patients with rare diseases in Europe. *Eur J Health Econ* 2016; 17: 1-5.
17. HAMMITT KM, NAEGELI AN, VAN DEN BROEK RWM, BIRT JA: Patient burden of Sjögren's: a comprehensive literature review revealing the range and heterogeneity of measures used in assessments of severity. *RMD Open* 2017; 3: e000443.
18. LACKNER A, FICJAN A, STRADNER MH *et al*.: It's more than dryness and fatigue: The patient perspective on health-related quality of life in primary Sjögren's syndrome - A qualitative study. *PLoS One* 2017; 12: e0172056.
19. NGO DYJ, THOMSON WM, NOLAN A, FERGUSON S: The lived experience of Sjögren's syndrome. *BMC Oral Health* 2016; 16: 7.
20. ROMÃO VC, TALARICO R, SCIRÈ CA *et al*.: Sjögren's syndrome: state of the art on clinical practice guidelines. *RMD Open* 2018; 4: e000789.
21. BALDINI C, FERRO F, ELEFANTE E, BOMBARDIERI S: Biomarkers for Sjögren's syndrome. *Biomark Med* 2018; 12: 275-86.
22. CALLAGHAN R, PRABU A, ALLAN RB *et al*.: Direct healthcare costs and predictors of costs in patients with primary Sjögren's syndrome. *Rheumatology* (Oxford) 2007; 46: 105-11.
23. MACIEL G, SERVIOLI L, NANNINI C *et al*.: Hospitalisation rates among patients with primary Sjögren's syndrome: a population-based study, 1995-2016. *RMD Open* 2018; 4: e000575.
24. MIYAMOTO ST, VALIM V, FISHER BA: Health-related quality of life and costs in Sjögren's syndrome. *Rheumatology* (Oxford). 2019 Feb 15 [Online ahead of print].
25. PERERA S, MA L, PUNWANEY R, RAMACHANDRAN S: Clinical and cost burden of primary Sjögren's syndrome: descriptive analysis using a US Administrative Claims Database. *J Health Econ Outcomes Res* 2018; 5: 150-61.
26. SEGAL B, BOWMAN SJ, FOX PC *et al*.: Primary Sjögren's Syndrome: health experiences and predictors of health quality among patients in the United States. *Health Qual Life Outcomes* 2009; 7: 46.
27. RAMOS-CASALS M, TZIOUFAS AG, STONE JH, SISÓ A, BOSCH X: Treatment of primary Sjögren syndrome: a systematic review. *JAMA* 2010; 304: 452-60.
28. TZIOUFAS AG, GOULES AV: Limited efficacy of targeted treatments in Sjögren's syndrome: why? *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S27-8.
29. LEONARDO NM, MCNEIL J: Behçet's disease: is there geographical variation? A review far from the Silk Road. *Int J Rheumatol* 2015; 2015: 945262.
30. GATTA G, CICCOLALLO L, KUNKLER I, CAPOCACCIA R: Survival from rare cancer in adults: a population-based study. *Lancet Oncol* 2006; 7: 132-40.
31. FEENY DH, FURLONG WJ, TORRANCE GW *et al*.: Multi-Attribute and Single-Attribute Utility Functions for the Health Utilities Index Mark 3 System. *Medical Care* 2002; 40: 113-28.
32. MEKINIAN A, TENNENBAUM J, LAHUNA C *et al*.: Primary Sjögren's syndrome: central and peripheral nervous system involvements. *Clin Exp Rheumatol* 2020; 38 (Suppl. 126): S103-9.
33. CAMERON AC, TRIVEDI PK: Regression-based tests for overdispersion in the Poisson model. *J Econometrics* 1990; 46: 347-64.
34. MURRAY J: Likert data: What to use, parametric or non-parametric? *Int J Business Social Science* 2013; 4: 258-64.
35. NORMAN G: Likert scales, levels of measurement and the "laws" of statistics. *Adv Health Sci Educ* 2010; 15: 625-32.
36. PELL G: Use and misuse of Likert scales. *Med Educ* 2005; 39: 970.
37. MATHEWS PM, HAHN S, HESSEN M *et al*.: Ocular complications of primary Sjögren syndrome in men. *Am J Ophthalmol* 2015; 160: 447-52.
38. RAMÍREZ SEPÚLVEDA JI, KVARNSTRÖM M, BRAUNER S, BALDINI C, WAHREN-HERLENIUS M: Difference in clinical presentation between women and men in incident primary Sjögren's syndrome. *Biol Sex Differ* 2017; 8: 16.
39. QIN B, WANG J, YANG Z *et al*.: Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. *Ann Rheum Dis* 2015; 74: 1983-9.
40. FLORES-CHÁVEZ A, KOSTOV B, SOLANS R *et al*.: Severe, life-threatening phenotype of primary Sjögren's syndrome: clinical characterisation and outcomes in 1580 patients (GEAS-SS Registry). *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S121-9.
41. AFILALO J, MARINOVICH A, AFILALO M *et al*.: Nonurgent emergency department patient characteristics and barriers to primary care. *Acad Emerg Med* 2004; 11: 1302-10.
42. BIANCO A, PILEGGI C, ANGELILLO IF: Non-urgent visits to a hospital emergency department in Italy. *Public Health* 2003; 117: 250-5.
43. CARRET ML, FASSA AG, KAWACHI I: Demand for emergency health service: factors associated with inappropriate use. *BMC Health Serv Res* 2007; 7: 131.
44. LEE A, LAU FL, HAZLETT CB *et al*.: Factors associated with non-urgent utilization of Accident and Emergency services: a case-control study in Hong Kong. *Soc Sci Med* 2000; 51: 1075-85.
45. OKTAY C, CETE Y, ERAY O, PEKDEMIR M, GUNERLI A: Appropriateness of emergency department visits in a Turkish university hospital. *Croat Med J* 2003; 44: 585-91.
46. ENGER TB, PALM Ø, GAREN T, SANDVIK L, JENSEN JL: Oral distress in primary Sjögren's syndrome: implications for health-related quality of life. *Eur J Oral Sci* 2011; 119: 474-80.
47. KOÇER B, TEZCAN ME, BATUR HZ *et al*.: Cognition, depression, fatigue, and quality of life in primary Sjögren's syndrome: correlations. *Brain Behav* 2016; 6: 1-11.
48. LENDREM D, MITCHELL S, MCMEEKIN P *et al*.: Health-related utility values of patients with primary Sjögren's syndrome and its predictors. *Ann Rheum Dis* 2014; 73: 1362-8.
49. BOWMAN S, BOOTH D, PLATTS R: Measurement of fatigue and discomfort in primary Sjögren's syndrome using a new questionnaire tool. *Rheumatology* 2004; 43: 758-64.
50. STROMBECK B, EKDAHL C, MANTHORPE R, WIKSTROM I, JACOBSSON LT: Health-related quality of life in primary Sjögren's syndrome, rheumatoid arthritis and fibromyalgia compared to normal population data using the SF-36. *Scand J Rheumatol* 2000; 29: 20-8.
51. SUTCLIFFE N, STOLL T, PYKE S, ISENBERG DA: Functional disability and end-organ

damage in patients with systemic lupus and Sjögren's syndrome. *J Rheumatol* 1998; 25: 63-8.
52. PERS YM, VALSECCHI V, MURA T *et al*.: A randomized prospective open-label controlled trial comparing the performance of a connected monitoring interface versus physical routine monitoring in patients with rheumatoid arthritis. *Rheumatology* (Oxford) 2021; 60: 1659-68.
53. RAMOS-CASALS M, BRITO-ZERÓN P, SISÓ-ALMIRALL A, BOSCH X, TZIOUFAS AG: Topical and systemic medications for the treatment of primary Sjögren's syndrome. *Nat Rev Rheumatol* 2012; 8: 399-411.
54. KNIGHT AW, SENIOR TP: The common problem of rare disease in general practice. *MJA* 2006; 185: 82-83
55. DOUGLAS L: Facilitating timely diagnosis of Sjögren's syndrome. *BDJ Team* 2018; 5: 18026.
56. GRABER ML, WATCHER RM, CASSEL CK: Bringing diagnosis into the quality and safety equations. *JAMA* 2012; 308: 1211-2.