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Original Article

Primary Sjögren's syndrome in Italy: Real-world evidence of a rare disease through administrative healthcare data

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ABSTRACT

Objectives: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease with significant impact on morbidity, mortality, and quality of life. This study aimed to evaluate epidemiology, healthcare needs and related costs of pSS patients from the Italian National Health Service perspective.
Methods: From the Fondazione Ricerca e Salute's database (~5 million inhabitants/year), pSS prevalence in 2018 was calculated. Demographics, mean healthcare consumptions and direct costs at one year following index date (first in-hospital diagnosis/disease waiver claim) were analysed through an individual direct matched pair case-control analysis (age, sex, residency).
Results: In Italy, 3.8/10,000 inhabitants were identified as affected by pSS (1,746 case: 1,746 controls) in 2018. In the year following index date, 53.7% of cases and 42.7% of controls received ≥1 drug ($p<0.001$); mean per capita cost was €501 and €161, respectively ($p<0.01$). At least one hospitalization occurred to 7.8% of cases and 3.9% of controls ($p<0.001$) with mean per capita costs of €416 and €129, respectively ($p = 0.46$). At least one outpatient specialist service was performed in 49.8% of cases and 30.6% of controls ($p<0.001$); mean per capita costs were €200 and €75, respectively ($p<0.01$). Overall, mean annual costs were €1,171 per case and €372 per control ($p < 0.01$).
Conclusion: According to results of this population-based study, the prevalence of pSS in Italy appears to be consistent with the definition of rare disease. Patients with pSS have higher pharmacological, in-hospital and outpatient specialist care needs, leading to three-times higher overall cost for the INHS, compared to the general population.

1. Introduction

Primary Sjögren's syndrome (pSS) is a chronic systemic autoimmune disease with a protean clinical phenotype ranging from very mild manifestations of dry eye and dry mouth to life-threatening major organ involvement and damage [1]. It mostly affects females with a female: male ratio of 9–20:1 and can present as a single disease or associated to other autoimmune conditions, such as rheumatoid arthritis and systemic lupus erythematosus [2,3]. Despite the course of pSS is generally indolent and usually not requiring systemic immunosuppressive therapies, even mild forms of the disease almost inevitably detrimentally affect patients' quality of life [4]. Moreover, the associated costs and work disability are remarkable and represent a direct consequence of delayed disease diagnosis, generalized pain and reduced physical function characterizing pSS patients [4]. Along with disease-related complications and extra-glandular involvement, these patients suffer from higher prevalence of multiple comorbidities, including cardiovascular (CV) diseases [5–7], and cancer [8].

Prevalence of pSS is highly variable, ranging from 0.013% [9] to 3.5% [10,11]. This variability may be due to numerous factors, including how pSS is defined (e.g., different sets of classification criteria and data sources), the study design (e.g., population-based vs. sample

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surveys), and the heterogeneity in genetic background and geographical setting of studied populations. Few studies analysing socio-economic aspects of pSS are currently available, showing consistent results of significantly increased healthcare services utilization, medication use, and costs, likely due to both the characteristics of the disease and associated comorbidities. Indeed, most studies show that pSS patients have about 2 to 3-times higher healthcare related costs compared to the general population [12–15]. Given the limited and heterogeneous literature about prevalence and healthcare consumption and costs of pSS patients coming from few countries, data are scarcely comparable. As far as we know, no real-world data studies on pSS have been published on the Italian population.

This observational retrospective study of Italian administrative healthcare data aimed to raise awareness of the prevalence of pSS and its direct burden on the Italian National Health Service (INHS), in terms of healthcare delivered and costs.

2. Materials and methods

2.1. Data source

This study originates from the cross linkage of the administrative healthcare data routinely collected in the Fondazione Ricerca e Salute's (ReS) database, under specific agreements with several Italian local and regional Health Authorities (HAs). These data are the same that Italian HAs periodically convey to the Ministry of Health for reimbursement purposes. Since the INHS is a universal coverage healthcare system, the administrative data collected by the HAs are potentially representative of the healthcare of all the INHS beneficiaries. Following this, given that the ReS database includes a large Italian community sample and age distributions have been demonstrated superimposable with those reported for the entire country by the Italian Institute of Statistics (ISTAT) [16], its reliable representativeness of the Italian population has allowed to conduct several observational retrospective studies on a range of clinical questions [17–19] since 2018 when Fondazione ReS was established with the aims of integrating findings from clinical trials and registries, and contributing to complete evidence-based and patient-centred clinical and policy choices. The ReS database includes the following administrative databases. The demographics database contains age, sex, HA of residency and disease waiver claim for co-payment for local and in-hospital outpatient specialist services and/or treatment dispensations. The pharmaceutical dataset consists of all drugs reimbursed by the INHS and supplied by local and hospital pharmacies: active substances can be analyzed by Italian marketing code, Anatomical Therapeutic Chemical code (World Health Organization's ATC classification [20]), dose, package number and dispensing date. The hospitalization database is analysable through in-hospital diagnoses and procedures recorded in the hospital discharge forms related to overnight and daily hospitalizations (Italian version of the 9th International Classification of Disease - Clinical Modification – ICD-9-CM) [21]. The outpatient specialist care dataset is composed by examinations, diagnostics and invasive/non-invasive procedures performed in local facilities affiliated with the INHS and are analyzed based on the related current national classification system. Given the reimbursement purposes, Italian administrative healthcare databases also include all costs directly paid by the INHS. The ReS database is physically placed into Cineca's servers [22], whose collaboration guarantees compliance with international standard certifications of data quality and security. Indeed, data are anonymized at the source and analyzed in aggregated form, according to the specific agreements with the HAs, owners of the data, and to European privacy laws. For these reasons and the institutional purposes of this study, neither informed consent nor ethical approval were applicable. Datasets and information about the HAs owners of the data are not available, neither publicly nor under request, because of the specific agreement terms.

2.2. Cohort identification

From the 2018 ReS database (about 8% of the Italian population beneficiary of the INHS care), among people analysable until 2013, those with at least one in-hospital primary or secondary diagnosis of SS (ICD-9-CM code: 710.2) in the hospital discharge form or with the specific disease waiver claim for co-payment (code: 030) were identified as affected by SS in 2018. To reduce the risk of including patients with potentially overlapping diagnoses, those meeting the criteria (supplementary Table 1) identifying head and neck cancer, hepatitis C, human immunodeficiency virus infection, sarcoidosis, amyloidosis and graft versus host disease, within the 5-year look-back period, were excluded. Furthermore, to improve the identification of patients with pSS, those with autoimmune disorders potentially associated with a secondary SS (rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, other connective tissue diseases; supplementary Table 2) within the 5-year look-back period were excluded.

The date of the first in-hospital diagnosis or disease waiver claim in 2018 was considered as the index date.

2.3. Demographics, healthcare resource consumption and direct healthcare costs

Patients with pSS were described by age and sex at index date.

An individual direct matched pair case-control analysis (controls selected randomly) was performed to assess the mean healthcare resource consumptions and the mean annual direct costs. Matched variables were sex, age, and local HA of residency. Cases were patients with pSS and controls were people who did not meet pSS identification criteria.

Case and controls were analysed for one year after the index date, in terms of:

- concomitant drugs supplied (patient distribution, consumption as mean defined daily dose – DDD, and mean per capita cost incurred by the INHS);
- overnight hospitalizations (patient distribution by main diagnosis, mean number of hospitalizations and days of in-hospital stay, and mean per capita cost incurred by the INHS);
- local outpatient specialist services (patient distribution, mean number of services, and mean per capita cost incurred by the INHS);
- mean per capita total cost incurred by the INHS and proportion of each cost item on the total expenditure.

Only INHS direct costs due to reimbursed pharmaceuticals, hospitalizations and local outpatient specialist services are recorded in the Italian administrative databases. Specifically, pharmaceutical costs were extrapolated from prices of community and hospital pharmacies (inclusive of value-added tax). The in-hospital expenditure was derived by the DRG (diagnosis related group) system tariffs, which is used to estimate the hospitalization and the in-hospital stay costs per patient, for the INHS reimbursement. Each DRG code corresponds to the overall in-hospital care (from admission to discharge) in their entirety and complexity, without distinguishing single performed services. Costs for local outpatient diagnostics and invasive/non-invasive procedures were assessed through the current national tariffs.

2.4. Statistical analyses

Differences of prevalence for binary variable were assessed by Chi-squared test of Fisher's exact test, as appropriate. Differences between continuous variables were evaluated with Mann-Whitney U test. Data were considered significant for $p < 0.05$. Significance levels were indicated with * for $p < 0.05$, ** for $p < 0.01$ and *** for $p < 0.001$.

Data extraction and analyses were performed by means of Oracle SQL Developer Italian version 18.1.0.095 (California, United States) and

Excel (Microsoft Office 365).

3. Results

Starting from a population of about 5 million inhabitants in 2018, in Italy, 1746 patients with pSS were identified (Fig. 1), with a prevalence of 3.8 per 10,000 inhabitants.

Most patients with pSS were females (1635/1746; 93.6%). The mean age was 61±13 years. Indeed, the highest prevalence was seen among patients aged 60–69, for both women (15.1 per 10,000) and men (1.2 per 10,000) (Fig. 2).

3.1. Healthcare resource consumption and direct costs among cases and controls

Within the follow-up year, at least one pharmacological treatment was dispensed to 53.7% of cases (997/1746) and 42.7% of controls (746/1746) ($p < 0.001$) with a mean annual cost of € 501 per case and € 161 per control ($p < 0.01$) (Fig. 3 and Table 1). Antibacterials for systemic use were the most supplied to both cases and controls. Immunosuppressants accounted for the highest cost of the total expenditure per case (€ 75/501; 15.0%), while agents acting on the renin-angiotensin system per control (€ 20/161; 12.3%).

At least one hospitalization occurred to 7.8% of cases (137/1746) and 3.9% of controls (68/1746) ($p < 0.001$), with a mean annual cost of € 416 per case and € 129 per control ($p = 0.46$) (Fig. 3 and Table 2). The most common causes of hospitalization were "diffuse diseases of connective tissue" among cases (34/1746; 1.9%) and "cholelithiasis" among controls (3/1746; 0.2%). On average, each case was admitted more frequently (1.5 vs 1.3 times) during the follow-up year and stayed in-hospital longer (14.3 vs 8.4 days) than controls.

At least one local outpatient specialist service was performed to 49.8% of cases (869/1746) and 30.6% of controls (534/1746) ($p < 0.001$) (Fig. 3, Table 3). In one year, on average, each case cost to the INHS € 200, while each control € 75 ($p < 0.01$). Cases and controls received, on average, 43 and 22 local outpatient specialist services during the follow-up year, respectively.

Overall, in the year following index date, the INHS spent € 1171 per case and € 372 per control ($p < 0.01$) (Fig. 3). Pharmaceuticals were likely to drive costs for both cases and controls.

4. Discussion

In this study, a very large representative sample of the Italian population was analysed to investigate the prevalence of pSS and its direct healthcare and economic impact on the INHS.

The prevalence of pSS in our Italian cohort was 3.8 per 10,000 inhabitants, which is consistent with the definition of rare disease [23]. Interestingly, this datum is in line with the majority of previously published data from population-based studies, but slightly lower than those obtained by sample design studies [11]. This observation is also confirmed by a meta-analysis including data from studies performed on European, Asian and South American cohorts, that reported an overall pSS prevalence of 6.1 per 10,000 inhabitants which resulted slightly

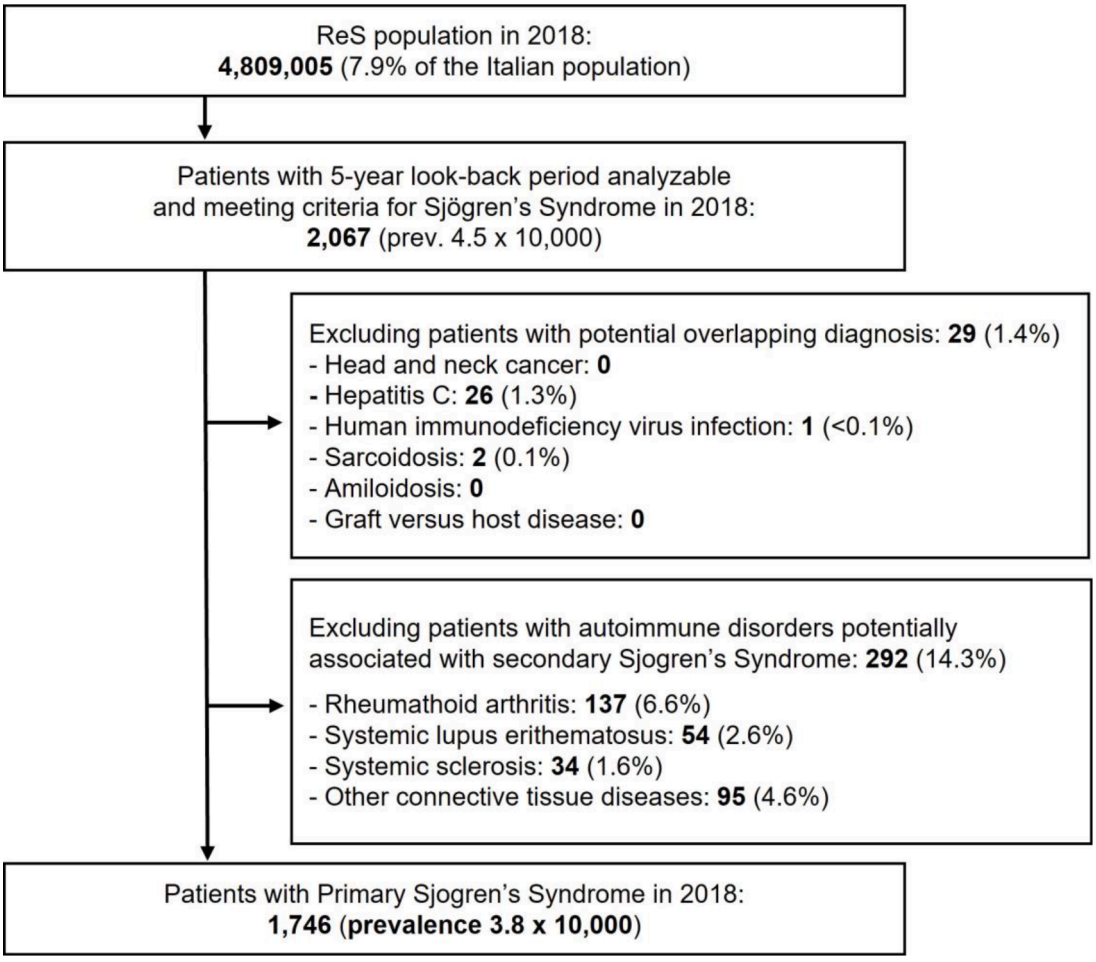

Fig. 1. Identification of patients with primary Sjögren's syndrome in 2018 from Fondazione Ricerca e Salute's database.
The flowchart shows the identification of patients with pSS in 2018 from the Fondazione Ricerca e Salute's database, meeting inclusion and exclusion criteria.

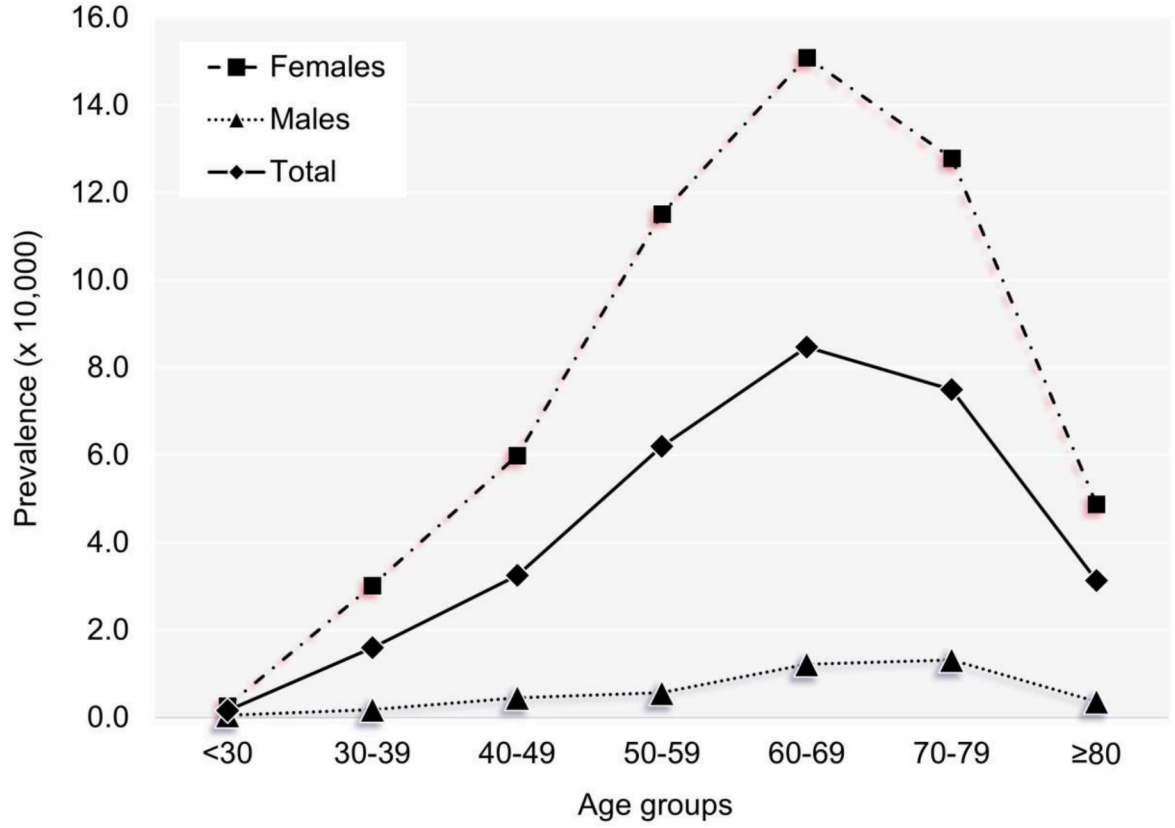

Fig. 2. Prevalence (per 10,000 inhabitants) of primary Sjögren's syndrome, by sex and age group.
The graph shows prevalences per 10,000 inhabitants, by sex and age group. Prevalences were higher for females than males with maximum values in the 60–69 age group.

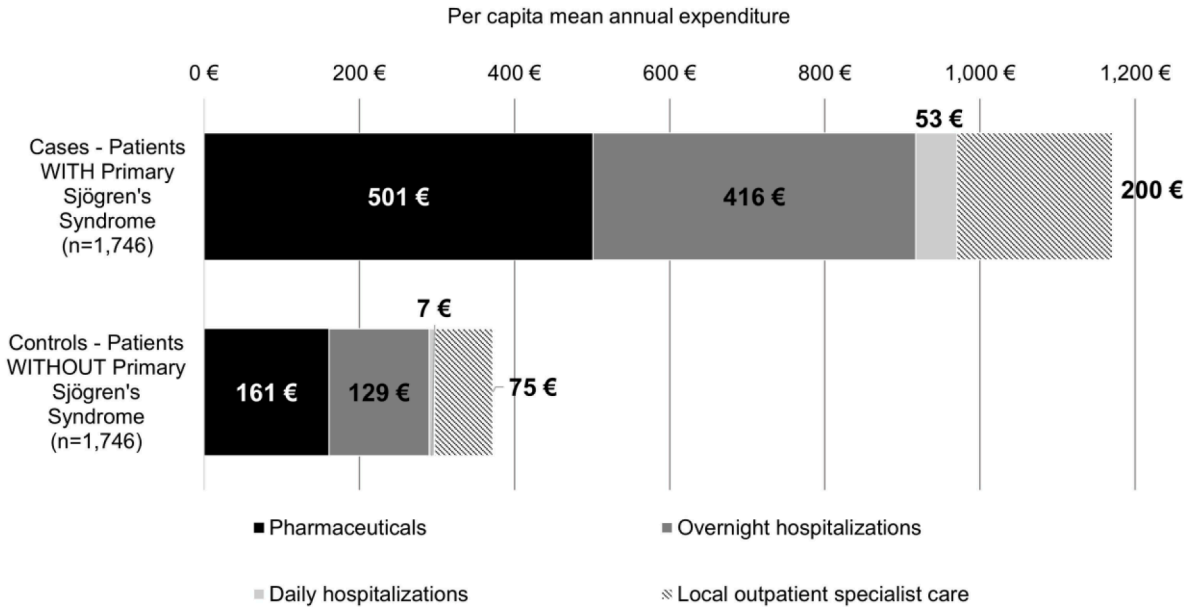

Fig. 3. Integrated healthcare costs incurred by the Italian National Health Service. Patients with pSS (cases) weighed on the Italian National Health Service more than patients without pSS (controls) for medications, hospitalizations, and outpatient services.

lower (4.3 per 10,000 inhabitants) when only population-based studies were considered [10].

The mean age of the patients enrolled in this study (61±13 years) was consistent to that reported in similar studies, ranging between 51 and 64.3 years of age. The female-to-male ratio of about 14.6 was slightly higher than most published reports, though well within the range of 9–20 that is considered typical of pSS [10,12–15,24,25]. These data support the goodness of the sample included in this study and its representativeness of the overall pSS patient population, thus the reliability of the results obtained.

Table 1
Pharmacological treatments (first 15 in decreasing order) among cases and controls during one-year follow-up. All top fifteen drug categories, except for agents acting on renin-angiotensin system, were used significantly more by pSS patients than controls.

Therapeutic group	Cases WITH Primary Sjögren's Syndrome ($n = 1746$)				Controls WITHOUT Primary Sjögren's Syndrome ($n = 1746$)			
	Patients treated (n; %)	Mean annual consumption (DDD/ treated patient)	Mean per capita annual cost (€)	% of total expenditure for drugs	Patients treated (n; %)	Mean annual consumption (DDD/ treated patient)	Mean per capita annual cost (€)	% of total expenditure for drugs
Antibacterials for systemic use	664; 38.0***	18.5	14	2.8	485; 27.8	15.3	8	5.2
Antacids	622; 35.6***	168.7	34	6.7	297; 17.0	114.5	11	6.8
Vitamins	546, 31.3***	523.7	17	3.3	175; 10.0	410.6	4	2.6
Corticosteroids for systemic use	525; 30.1***	109.8	10	1.9	129; 7.4	41.8	1	0.5
Non-steroidal anti-inflammatory and anti-rheumatic drugs	483; 27.7***	55.3	7	1.4	359; 20.6	45.2	4	2.5
Antiprotozoals	465; 26.6***	113.4	16	3.1	8; 0.5	4.7	0	0.0
Ophtalmologicals	419; 24.0***	249.3	24	4.7	25; 1.4	255.2	2	1.1
Agents acting on renin-angiotensin system	270; 15.5	349.9	19	3.8	279; 16.0	376.6	20	12.3
Drugs for obstructive airway diseases	228; 13.1***	77.0	19	3.8	144; 8.2	81.3	9	5.5
Thyroid therapy	224; 12.8***	167.1	3	0.5	94; 5.4	176.6	1	0.7
Antithrombotic agents	214; 12.3***	205.4	13	2.6	149; 8.5	193.0	7	4.6
Beta-blockers	180; 10.3*	152.6	5	1.1	145; 8.3	183.9	5	3.1
Analgesics	161; 9.2***	22.8	6	1.2	70; 4.0	18.1	1	0.9
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	152; 8.7***	27.9	3	0.6	69; 4.0	58.3	3	2.1
Immunosuppressants	151; 8.6***	131.9	75	15.0	7; 0.4	141.7	11	7.0
At least one drug	937; 53.7***	1282.3	501	100.0	746; 42.7	685.8	161	100.0

Variables marked are significantly different compared to controls (*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$).

A proportion of 53.7% pSS patients (vs 42.7% controls) were supplied with at least one drug during the follow-up year. The larger number of patients taking corticosteroids, antiprotozoals (likely driven using anti-malarias), ophtalmologicals, analgesics and immunosuppressants was expected as direct consequence of pSS treatment. Nevertheless, the differences in other therapeutic groups deserve some discussion. The very common use of antibacterials may be due to a higher prevalence of infection risk (e.g., of tuberculosis, bacterial pneumonia, and urinary tract infections), which has been previously demonstrated in pSS, and represents the second cause of death after CV events [26]. However, it is worth underlining that this excess prevalence of infections was likely due to the use of immunosuppressive treatments, rather than by the pSS itself [8]. Similarly, the higher use of drugs for obstructive airway diseases and for thyroid disease may represent the consequence of airway and lung involvement associated with pSS, along with the higher prevalence of autoimmune thyroid disease in these patients [13,24].

Interestingly, the percentage of patients taking non-steroidal anti-inflammatory drugs (NSAIDs), topical ophthalmological drugs, and hydroxychloroquine are very close to those recently described in a pSS cohort in the community of Madrid (27.7% vs. 28.9%, 24.0% vs. 32.4%, and 26.6% vs. 17.4%, respectively). On the contrary, the use of corticosteroids was higher in our cohort (30.1% vs. 15.6%) [24]. However, the use of medication was overall lower than studies where patients with SS associated with other systemic autoimmune diseases were also included [12,24]. Indeed, comparison with other studies is challenging, mostly due to different data sources and the presentation of findings [14]. Mean per pSS patient annual cost for all pharmacological treatments (disease-related and non-disease related) was three-times higher than controls. This finding suggests that higher use of non-pSS related medications may actually be influenced by the disease itself, both directly due to higher prevalence of comorbidities (e.g., cardiovascular disease) and indirectly, as a consequence of its treatment (such as infections induced by immunosuppressors).

Cases were hospitalized more frequently than controls (7.8% vs. 3.9%), and mean overall costs for hospitalization were 3.2 times higher in pSS, in line with other published reports showing ratios ranging between 3.4 and 3.8 [13,15].

It is worth noticing that the mean length of hospital stay was significantly longer in cases than in controls (14.3 vs. 8.4 days), regardless of the cause of hospitalization. This could suggest that the presence of pSS may make diagnosis and therapy set-up more challenging in hospitalized patients. The main reason of hospitalization cases was "diffuse diseases of connective tissue", likely reflecting flares of the disease itself. The very low frequency of hospitalizations, including those probably independent of pSS, prevented any reliable comparison with data obtained in the general population, though suggesting a potential contribution of comorbidities.

At the same time, the overall low rate of hospitalization could also partly reflect that most medical complaints in pSS patients may be adequately managed in outpatient settings. This is also suggested by the significant higher rate of local outpatient services in these patients, likely due to disease-related concerns, such as laboratory tests, eye examinations, diagnostic of head and neck, chest, and musculoskeletal imaging (Table 3). However, a higher rate of electrocardiogram, abdomen and breast imaging prescription was observed in pSS, as well.

Table 2
Hospitalizations (first 15 primary diagnoses in decreasing order) among cases and controls during one-year follow-up. More pSS patients were hospitalized compared to controls, mostly due to disease-flares.

Primary in-hospital diagnosis (ICD-9-CM code)	Cases WITH Primary Sjögren's Syndrome ($n = 1746$)					Controls WITHOUT Primary Sjögren's Syndrome ($n = 1746$)				
	Hospitalized patients (n;%)	Hospitalizations/ hospitalized patient (n)	Mean length of in-hospital stay (days)	Mean per capita annual cost (€)	% of total expenditure for hospitalizations	Hospitalized patients (n;%)	Hospitalizations/ hospitalized patient (n)	Mean length of in-hospital stay (days)	Mean per capita annual cost (€)	% of total expenditure for hospitalizations
Diffuse diseases of connective tissue	34; 1.9***	1.0	10.8	66	15.8	0; 0.0	–	–	–	–
Cholelithiasis	5; 0.3	1.0	5.2	10	2.4	3; 0.2	1.0	4.0	3	2.6
Chronic renal failure	4; 0.2	1.0	7.5	7	1.6	0; 0.0	–	–	–	–
Other diseases of lung	4; 0.2	1.8	21.0	18	4.2	1; 0.1	1.0	2.0	2	1.7
Intestinal obstruction without mention of hernia	3; 0.2	1.0	10.3	7	1.7	0; 0.0	–	–	–	–
Cardiac dysrhythmias	3; 0.2	1.0	7.7	4	1.0	1; 0.1	2.0	4.0	1	0.5
Nontoxic nodular goiter	3; 0.2	1.0	4.3	5	1.3	0; 0.0	–	–	–	–
Occlusion of cerebral arteries	3; 0.2	1.0	11.0	7	1.6	0; 0.0	–	–	–	–
General symptoms	3; 0.2	1.3	10.3	4	0.9	2; 0.1	1.0	36.5	6	4.8
Diseases of the salivary glands	3; 0.2	1.0	8.0	2	0.4	0; 0.0	–	–	–	–
Unspecified peripheral vascular disease	3; 0.2	1.0	7.7	6	1.4	0; 0.0	–	–	–	–
Heart failure	3; 0.2	1.7	17.7	9	2.1	2; 0.1	1.0	13.5	4	2.8
Unspecified noninfectious gastroenteritis and colitis	2; 0.1	1.0	8.0	2	0.6	0; 0.0	–	–	–	–
Unspecified disorders of bladder	2; 0.1	1.0	6.0	5	1.2	0; 0.0	–	–	–	–
Rheumatoid arthritis and other inflammatory polyarthropathies	2; 0.1	1.0	8.0	3	0.8	1; 0.1	1.0	15.0	2	1.8
At least one hospitalization	137; 7.8***	1.5	14.3	416	100.0	68; 3.9	1.3	8.4	129	100.0

Variables marked are significantly different compared to controls (*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$).

Table 3
Outpatient specialist services (first 10 in decreasing order) among cases and controls during one-year follow-up. More pSS patients required outpatient services compared to controls. Differences were significant for all top ten service categories.

Local outpatient specialist service (national classification)	Cases WITH Primary Sjögren's Syndrome ($n = 1746$)				Controls WITHOUT Primary Sjögren's Syndrome ($n = 1746$)			
	Outpatients (n;%)	Specialist service/ outpatient (n)	Mean per capita annual cost (€)	% of total expenditure for outpatient services	Outpatients (n;%)	Specialist service/ outpatient (n)	Mean per capita annual cost (€)	% of total expenditure for drugs
Laboratory test	755; 43.2***	36.7	64	32.1	360; 20.6	23.4	19	24.8
General examination	647; 37.1***	3.6	22	10.9	304; 17.4	2.5	8	10.1
Eye examination	244; 14.0***	1.8	5	2.5	51; 2.9	1.5	1	1.2
Diagnostic imaging head/ neck	180; 10.3***	1.4	6	3.2	45; 2.6	1.2	1	1.8
Electrocardiogram	179; 10.2***	1.3	3	1.3	67; 3.8	1.4	1	1.4
Diagnostic imaging abdomen	134; 7.7***	1.4	8	3.9	51; 2.9	1.4	3	4.2
Diagnostic imaging muscoloskeletal	132; 7.6***	1.9	7	3.6	54; 3.1	1.7	3	3.4
Diagnostic imaging chest	126; 7.2***	1.3	5	2.3	31; 1.8	1.3	1	1.4
Diagnostic imaging breast	122; 7.0*	1.9	5	2.4	86; 4.9	1.7	3	4.1
Diagnostic imaging lower limb	111; 6.4***	2.5	4	1.9	53; 3.0	1.8	1	1.6
At least one outpatient service	869; 49.8***	42.7	200	100.0	534; 30.6	21.9	75	100.0

Variables marked are significantly different compared to controls (*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$).

Albeit a part of these instrumental test prescriptions can be explained by a major attention to the disease consequences by the physician, it is likely that a deeper awareness of comorbidities in these patients may exert the most significant impact. In particular, higher requests of electrocardiography may be an indirect effect of the significant CV morbidity characterizing pSS, which is supported by the data on hospitalizations for arrhythmias, cerebrovascular accidents and peripheral vascular disease [5,8,27]. Mean annual costs due to outpatient specialist services were significantly higher in cases than in controls. As expected by findings on costs per administrative flow, the mean per pSS patient overall integrated healthcare cost were three-times higher than controls.

4.1. Strengths and limitations

The main strengths of the study rely on the very large sample analysable through the ReS database, which is considered as representative of about 8% of the Italian population variously distributed from Northern to Southern Italy. The Italian population, at the same time, given that the INHS is a universal coverage health system, is also potentially representative of the whole INHS beneficiaries community. Moreover, as far as we know, this is the first study that assessed prevalence, healthcare needs and the economic burden of pSS in real-world settings coming from a large Italian sample, compared to the general population.

Some limitations should be acknowledged. First of all, due to the study design and data source, an accurate identification of cases was challenging as pSS patients could only be identified by an in-hospital diagnosis or by the specific disease waiver claim code. This did not guarantee that all patients included fulfilled classification criteria for pSS. Secondly, outpatients to whom the disease waiver claim code was not given, because they were affected by another disease granting them exemption from co-payment of healthcare services, may not have been included in the dataset. Another point to consider is that this study did not assess patients newly diagnosed with pSS; therefore, the index date could not correspond to the actual onset of this disease. Given the frequent diagnostic delay and the long and irregular intervals between pSS onset and the occurrence of clinical symptoms, complications may significantly and differently impact on healthcare costs. Additionally, possible cause of drug prescriptions can only be supposed, given the absence of the related diagnosis in administrative databases. Finally, also the out-of-pocket purchase of drugs and data from outpatient specialist services or hospitalizations occurring in private facilities (i.e., not affiliated with the INHS) are not reported in administrative databases.

5. Conclusion

In conclusion, this observational retrospective study on a large Italian real-world population confirmed that pSS prevalence is consistent with the definition of rare disease. We are aware that this statement should be considered with caution for the known limitations of population-based studies, although the huge number of included patients may support the reliability of our datum. In addition, in line with the few available studies, it highlighted the threefold higher burden of pSS patients than the general population in terms of healthcare resource consumption and direct INHS costs, likely due to both disease-related issues and higher prevalence of comorbidities.

These findings confirm the need for an appropriate and multidisciplinary approach to pSS by the Italian HAs, encompassing all aspects of patient care, by including early and accurate diagnosis, access to INHS health services and long-term follow-up.

CRediT authorship contribution statement

Giacomo Cafaro: Writing – original draft, Formal analysis. **Carlo Perricone:** Writing – original draft, Writing – review & editing. **Giulia Ronconi:** Conceptualization, Methodology. **Silvia Calabria:** Writing – original draft, Writing – review & editing, Methodology. **Letizia Dondi:** Conceptualization, Formal analysis, Data curation, Software. **Leonardo Dondi:** Formal analysis, Data curation, Software. **Antonella Pedrini:** Funding acquisition, Project administration. **Immacolata Esposito:** Project administration, Funding acquisition. **Roberto Gerli:** Writing – original draft, Writing – review & editing. **Elena Bartoloni:** Writing – original draft, Writing – review & editing. **Nello Martini:** Writing – original draft, Supervision.

Declaration of competing interest

The authors declare no conflicts of interest.

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Not applicable.

Ethics

This was a retrospective observational study of Italian administrative data which have been analysed in an aggregated form after their anonymization at the source, according to the specific agreements with the Regional/Local Health Authorities, owners of the data, and to the European privacy laws. For these reasons and because of the institutional purposes of this study, ethical approval was not applicable.

Data availability

The data underlying this article cannot be shared publicly due to being property of Italian Regional/Local Health Authorities who have not authorized the authors to make them available.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2024.02.010.

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