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An Early View of Iran Primary Sjogren Syndrome Registry (Guilan Province Pilot Phase), an Emerging Effort for a National Registry Establishment

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Abstract

Background: The Sjogren syndrome (SS) is the least well-known rheumatic condition. We aim to gradually resolve it by standardizing the process of SS care in our country, at first for primary Sjogren syndrome cases, through developing Iran Primary Sjogren Syndrome Registry (IRAPSS) which will create a representative and comparable data bank.

Methods: Guilan Primary Sjogren Syndrome Registry (GUIRAPSS) is a pilot phase of IRAPSS, which is a prospective cohort. Care of its patients is done based on EULAR Sjögren's syndrome disease activity index (ESSDAI) recommendations. Other IRAPSS outcome measurements are EULAR Sjogren syndrome patient reported index (ESSPRI) and Sjögren's syndrome disease damage index (SSDDI) for detecting disease damage.

Results: Female-male ratio was 17.5. The age at expert diagnosis was 46.97 ± 11.93 years old. The most common comorbidity was hypothyroidism (28.38%), followed by musculoskeletal conditions (27.02%). 28.38% had fatigue. Active disease existed based on the clinical form of ESSDAI and ESSDAI, 31.8% and 81.8% respectively. The most involved organs during disease activity based on ESSDAI were biological 68.12% following pulmonary (12.16%) and respiratory (10.81%) system. Hydroxychloroquine was the most prescribed drug (72.97%), followed by prednisolone (28.38%).

Conclusion: Disease registries provide an ideal opportunity for gathering standardized and comparable data which provides needed items for creating, updating, or adapting pSS classification criteria/diagnosis, outcome measurements and or treatment guidelines.

Keywords: Primary Sjogren, Sjogren, Registry

Conflicts of Interest: *None declared*
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↑What is "already known" in this topic:
Determinants of primary Sjogren syndrome (pSS) pathogenesis (the least well-known and a heterogenous rheumatology disease) are exogenous factors (such as viral infections, sex hormones, solvents and inorganic chemical components) that abnormally active the immune system in the genetically predisposed individuals. The role of these determinants may differ across various populations inhabiting diverse geographical locations and can result in various pSS phenotypes, treatment responses and final natural history.

→What this article adds:
We have both provided comprehensive and standardized data about the first unique sample of Persians with pSS and summarized the other largest pSS registry data to describe and propose some hypotheses about observed similarities and discrepancies.

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Introduction

Sjogren syndrome (SS) is one of the most common and the least well-known rheumatic conditions with significant economic and health burdens (1-4). SS which can occur with (secondary) or without (primary: pSS) other rheumatology diseases, is characterized by lymphocytic infiltration in exocrine glands especially in the mouth and eyes. Various other organs can also be involved. The pathophysiology resulting from different phenotypes (especially ones with extra glandular involvements) has not been well known yet. Unfortunately, there is not adequate high-quality evidence about pSS for example, about its treatment, especially about the Iranian population with pSS. The most important barrier is misclassification of patients presenting with one of pSS presentations (especially a more severe form of them) as ones who have other rheumatic diseases such as rheumatoid arthritis or systemic lupus erythematosus (5, 6). Without precise and accurate disease classification, studies that aim to define pSS phenotype or course or develop sensitivity to change outcome measurements should logically be considered at risk of important biases. Also, studies comparing different treatment interventions must be downgraded at the time of retrieving evidence for developing guidelines due to the risk of bias, imprecision, inconsistency and/or indirectness (7). Disease registries provide an ideal opportunity for resolving existing barriers in research and finally providing a representative large sample size. Our aim is to report characteristics, phenotypes and severity of pSS in patients registered in the pilot phase of Guilan primary Sjogren syndrome as it is an emerging effort for the establishment of a national registry.

Methods

Guilan Primary Sjogren Syndrome Registry (GUIRAPSS) is a primary data source for prospectively gathering a standardized minimum data set of patients with pSS. We are highly focused on designing a qualified real-world minimum data set registry that is easily adoptable in provinces with the least needed infrastructures for it. During the pilot phase, we used a risk-based approach to find threats that can influence our data quality and find ways to resolve and prevent their recurrence. Based on this approach, we updated our protocol, data dictionary, data collection forms, and quality assessment tools and finally, we are upgrading our website.

Guilan province has a humid subtropical climate located in the north of Iran, along the Caspian Sea (8). Almost all rheumatologists working in this province are gradually referring their patients with a diagnosis of primary Sjogren syndrome (Expert opinion is GUIRAPSS including criteria) to the GUIRAPSS clinic at Razi Teaching Hospital. After gathering patient characteristics, they were excluded if they did not meet either American-European Consensus Group Sjögren's syndrome classification (AECG) criteria or American College of Rheumatology/European League Against Rheumatism classification (ACR/EULAR) criteria for pSS (Excluding criteria) (9, 10). Classification was done based on available tests in pragmatic physician daily practice including anti-Ro antibody, anti-La antibody, ANA (antinuclear antibody by Immunofluorescence method), rheumatoid factor, Schirmer test I, Unstimulated Whole salivary flow test and minor salivary gland. Two first tests are done for all patients but the other tests are done based on rheumatologist decisions for checking registry exclusion criteria.

Before launching the pilot phase and during it, we were faced with the absence of Schirmer test strips in some Guilan ophthalmologist clinics. After assessing its reasons, we noticed that it could be owing to rare requests by other physicians, Covid 19 pandemic, ophthalmologist routines and/or unavailability of Schirmer strips (on account of Iran sanctions). Then based on rheumatologist expert opinion, in cases not assessing dry eye through the Schirmer test, to circumvent this obstacle, we added positive dry eye by slit lamp examination in our ophthalmologist consultation form, and if it they reported any degree of dry eye, we considered it as positive Schirmer test.

At first activity assessment visits, before any new treatment intervention(s), patients' drug history must be specified in the GUIRAPSS rheumatology form.

In GUIRAPSS, care of patients is done based on EULAR Sjögren's syndrome disease activity index (ESSDAI) which can be used as an outcome measurement. Other used outcome measurements are EULAR Sjogren syndrome patient reported index (ESSPRI is a patient-reported outcome (PRO)) for determining disease quality of life (dQOL) and Sjögren's syndrome disease damage index (SSDDI) for detecting disease damage and Clinical type of ESSDAI (clinESSDAI) (11-15).

In the three-year interval after the first disease activity visit, patients' data about activity, dQOL and damage will be registered. Between two GUIRAPSS visits care of all registered patients will be done in the GUIRAPSS clinic.

For detecting patients' comorbidities, we have asked this question: "Which diseases have been ever told you by a specialist or sub-specialist ,except to pSS, that you have, including ones that needed surgery, for example, hypothyroidism, diabetes mellitus, hypertension, hyperlipidemia, fibromyalgia and/or any cardiac, pulmonary, liver , gallbladder, biliary tract disease and so on?" Then for checking the correctness of the patient's answer, the patient's drug history and all medical documents were assessed.

For detecting familial history of malignancy, we have asked this question:" Do your relatives, including your parents, sister, brother, children, grandparents, Niece, Nephew, Aunt, Uncle, or grandchild have a positive history of malignancy?" If their answer was positive, we asked them to specify which one/s of them.

For determining "presenting symptom(s)", we asked patients, "Which complaint do you have when your rheumatologist has diagnosed your disease as pSS?" Fatigue was defined as "an inclination to rest even though pain and weakness are not limiting factors. Fatigue after varying degrees of activity that is relieved by rest is normal and was

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considered as No fatigue" (16). A low burden of fatigue, total dryness or joint or muscular pain was defined in the Tam et al. exploratory clustering analysis study (17).

For this early view, we have used descriptive statistical analysis, including relative frequency, mean, standard deviation, median and "25th - 75th interquartile range". After achieving an adequate sample size GUIRAPSS statistical plan uses appropriate statistical analysis to address long-term therapeutic outcomes (marginal structural modeling), predictors of recurrent flares (recurrent event modeling), determinants of disease progression (multistate modeling) and detecting similar groups of patients (cluster analysis, multiple correspondence analysis, and/or similarity network fusion).

Also, we used the Cochrane data extraction formula for some used studies in the discussion section (18).

In our report patient per population was calculated by dividing "the number of registered pSS cases by "the total population divided by 100000".

Results

During the pilot phase, 74 cases completed two first visits of IRAPSS (First classification and first activity visits: January 21, 2020 - January 21, 2023) and their data were completed for calculating clinESSDAI. The patient's geographic distribution has been demonstrated in Figure 1.

Disease duration in 29.72 % was less than 6 months. All patients had met ACR/EULAR criteria. 61 cases met the AECG criteria, for the other 13 cases. They could potentially meet AECG criteria only if:

1. In six patients , a minor salivary gland biopsy was positive
2. In one case, USWSFR is positive
3. In five cases, minor salivary gland biopsy or USWSFR is positive
4. In one case minor salivary gland biopsy or Schirmer test is positive

Their female-to-male ratio was 17.5, 48.65% were middle-aged (45 – 65 years old: at the time of expert diagnosis) and 9.46% were elderly (≥ 65 years old). 21.62% had a positive familial history of malignancy. There was polypharmacy (regular use of more than 5 drugs during the past 3 months) in 47.30% of cases. The median and 25-75 interquartile range of "number of drugs regularly used during past three months" was 5, 3-7. 18.9% of patients used benzodiazepines, tricyclic antidepressants, selective serotonin reuptake inhibitors and/or serotonin and norepinephrine reuptake inhibitors. Ten patients (13.51%) did not take any disease-modifying antirheumatic drugs (DMARDs). In the other patients, drugs that were used for pSS treatment, in descending order, were included hydroxychloroquine (HCQ) 72.97% , prednisolone 28.38%, methotrexate (MTX) 9.46% , azathioprine (AZA) 6.76% and leflunomide (LEF) 4.05%, mycophenolate mofetile (MMF) 1.35% and rituximab (RITUX) 1.35%. There were 16.22% allergies to at least one drug in 16.22% (10.8% to HCQ, 2.7% to MTX, 1.35% to alendronate and 1.35% to AZA). Other patient characteristics are shown in Table 1.

The eight most common presenting symptoms (64.86%), in descending order, were dry mouth 13.51%, arthralgia 13.51%, skin rashes (purpura, wheels, hyperpigmentation, and painful papules) 6.76%, dry eye 5.41%, arthritis 5.41%, salivary gland enlargement 5.41% , general pain 4.05% and combination of " dry mouth and dry eye" 4.05%. 6.76% were asymptomatic (diagnosed by experts because of high ESR, leukopenia or thrombocytopenia).

SICCA symptoms (dry eye and dry mouth) existed in 95.95% (81.8% dry eye and 81.08% dry mouth). Data about pSS cardinal (fatigue, total dryness, and pain) and SICCA symptoms have been demonstrated in Table 2. Between four symptom–based pSS subgroups, our patients cannot be grouped as high symptom burden, dryness dominant with fatigue, or pain dominant with fatigue. Only if data about the hospital anxiety and depression scale (HADS) was

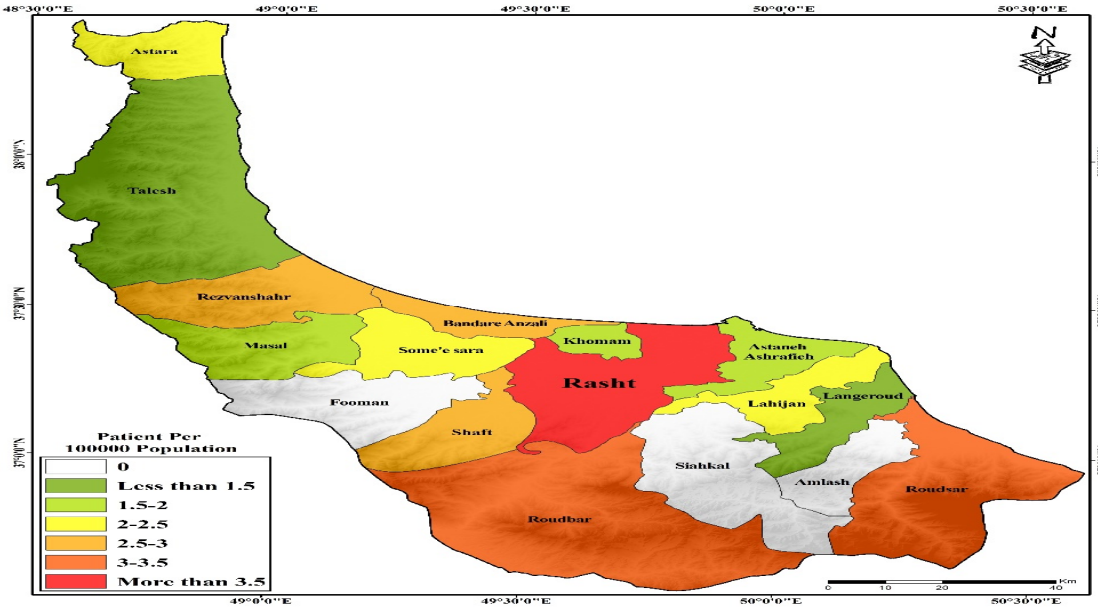

Figure 1. Distribution of enrolled patients in the pilot phase of the Guilan branch of Iran's primary Sjogren syndrome registry (GUIRAPSS)

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available would we have the ability to assess whether our patients were in the low symptom burden group or not.

Minor salivary gland biopsy (MSGB) was done for seven patients, which was positive in 6 cases. 97.3% were seropositive (positive Anti Ro Ab or Anti La Ab). In 58.11% of patients Anti Ro and Anti La. In 37.84% only Anti Ro and in 1.35% only Anti La were positive. Other information about these tests exists in Table 3.

At the first activity assessment visit ten patients did not use any DMARDs. Of them, based on clinESSDAI, only one case (Pulmonary involvement) had active disease, but based on ESSDAI, only one case had inactive disease (One case pulmonary and eight cases biological domain involvement). Based on ESSDAI organ involvement definitions, biological involvement was seen in 68.12%, pulmonary 12.16%, hematologic 10.81%, articular 5.41%, glandular 6.76%, cutaneous 1.35% and renal 1.35%. There were no lymphadenopathy or nervous system involvements. Other information about patient disease activity and prognostic factors which have been suggested in previous studies, has been summarized in Table 3. Most patients (85.14%) had good pSS-related quality of life (patients acceptable symptoms score or PASS: ESSRI ≥5) with mean, standard deviation 2.51 ± 2.28 and median, 25-75 IQR 1.7, 1-3.33.

Discussion

We presented the data of the pilot phase of the Guilan

Table 1. Characteristics in patients registered in the pilot phase of Iran's primary Sjogren syndrome registry (Guilan province) at first disease activity assessment visit

Characteristics	Statistic Percentage (%) / Mean ± Standard deviation / [# missing cases]
Female	94.59%
Age at expert diagnosis (AgeEx)	46.97 ± 11.93 year
Age at registration	50.13 ± 11.58 year
Education (years)	10.68 ± 5.08 year
Job situation	Housewife (67.57%), Working (21.62%), Retired (9.49%), Student (1.35%)
Marital status	Single (4.05%), Married (95.95%)
Smoking situation	Never smoke (97.30%), Current smoking (1.35%), Ex-smoker (1.35%)
Alcohol/illicit drug users	No one
Menopause	51.42 %
FH of malignancy only in first-degree	4.05 %
FH of malignancy only in second-degree	12.16 %
FH of malignancy in both degrees	5.41 %
Ten most common comorbidities[1]	Hypothyroidism (28.38 %), Musculoskeletal conditions [2] (27.02%), Hypertension (24.32 %), Hyperlipidemia (14.86 %), Fibromyalgia (10.81 %), Nephrolithiasis (8.11 %), Diabetes mellitus (8.10 %), Fatty liver (6.76%), Gallbladder conditions (6.76%), Minor thalassemia (4.05%)
Polypharmacy Score[3]	5.20 ± 2.72
DMARDs	HCQ (64.86%), MTX (8.11%), HCQ+AZA (5.41%), LEF (1.35%),LEF+HCQ (1.35%), LEF+MTX (1.35%), HCQ+MMF (1.35%), AZA (1.35%), RITUX (1.35%)

[1]. There was no missing case except for osteoporosis .In the patients past medical history, there was one case of myasthenia gravis, one case of paraparesis, one case of lichen planus, one case of breast cancer, two cases of chronic kidney disease (not related to pSS: one due to NSAIDs and the other due to lithium-based on nephrologist consultation), one case of myasthenia gravis, one case of G6PD deficiency
[2]. Osteoporosis: 12.09% [42 cases don't have or didn't do bone densitometry].
[3]. Number of medications at the time of first activity visit.

Table 2. SICCA and cardinal symptoms in patients registered in the pilot phase of Iran's primary Sjogren syndrome registry (Guilan province) at classification and first disease activity assessment visits, respectively

Symptoms	Statistic Percentage (%) / Mean ± Standard deviation / Median, 25 - 75 interquartile range / [# missing cases][1]
Ophthalmic SICCA symptoms:	
Have you had daily, persistent, troublesome, dry eyes for more than 3 months?	60.81 %
Do you have a recurrent sensation of sand or gravel in the eyes?	72.97 %
Do you use tear substitutes more than 3 times a day?	54.05 %
Oral SICCA symptoms:	
Have you had a daily feeling of dry mouth for more than 3 months?	63.51 %
Have you had recurrently or persistently swollen salivary glands as an adult?	32.43 %
Do you frequently drink liquids to aid in swallowing dry food?	60.81 %
Cardinal symptoms[2]:	
Fatigue	28.38%, 2.07 ±3.46/ 0, 0-5
Total dryness	77.03% , 4.58 ±3.29 / 5, 3-7
Pain	8.11%, 0.75 ± 2.44 / 0, 0-0
Low fatigue burden (Fatigue VAS ≤ 3)	71.62 %
Low dryness burden (Total dryness VAS ≤ 4)	35.14 %
Low pain burden (Joint or muscular pain VAS ≤ 2)	90.54 %

[1]. There was no missing case.
[2]. During the past two weeks.

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Table 3. Outcomes (clinESSDAI, ESSDAI and PASS) and prognostic factors in patients registered in the pilot phase of Iran's primary Sjogren syndrome registry (Guilan province).

Outcomes / Prognostic factors	Statistic Percentage (%) / Mean ± Standard deviation / Median, 25 - 75 interquartile range / [# missing cases]
Disease activity:	
Active disease based on clinESSDAI (score ≥1)	31.08 %
clinESSDAI score	6.75 ± 15.39 / 0, 0-6
Active disease based on ESSDAI (score ≥1)	81.8 % (5)
ESSDAI score	7.66 ± 13.96 / 2, 0-6, [5]
Pattern of organ involvements due to disease activity [2] :	
Only hematologic	8.11 %
Only respiratory	8.11 %
Only glandular	5.41 %
Only articular	2.70 %
Respiratory and articular	2./70 %
Renal and glandular	1.35 %
Respiratory and Hematologic	1.35 %
Cutaneous and hematologic	1.35 %
Suggestive prognostic factors based on available previous studies:	
Male	5.41 %
Disease duration (DDEx – at expert diagnosis)	3.14 ± 4.64 year / 1.5, 0.2- 4 year
Early onset disease (DDEx ≤ 3 years , < 5 years)	70.27 %, 79.73%
Early onset disease (AgeEx ≤ 35 years old)	17.57%
Late-onset disease (AgeEx ≥ 65 years old)	9.46%
Parotidomegally	6.76 %
ILD	5.41 %
Vasculitis	1.35 %
Positive Anti Ro Antibody[3]	95.95 %
Positive Anti La Antibody[3]	50.46 %
Positive Rheumatoid Factor[4]	75.38 % (9)
Low C3	16.44 % (1)
Low C4	2.74 % (1)
Low CH50	No one (8)
Hyper gammaglobulinemia	50.68 (1)
Hypo gammaglobulinemia	4.11 % (1)
IgG> 16 mg/dl	12.67% (3)
Cryoglobulinemia	No one (4)

[1]. Outcome measurement score ≥ 1.
[2]. Based on clinESSDAI.
[3]. Cumulative frequency at the time of classification visit.
[4]. Cumulative frequency at the time of first activity assessment visit.

province IRAPSS registry, an effort to obviate an unmet national health care, education and research system that will be appropriately provided by a national pSS registry. During the implementation of this phase, we noticed that considering real-world medical center daily practice, especially busy ones and accepting infrastructure, human and financial resource limitations are the most important clues in designing a qualified disease registry and in preventing from gathering a lot of useless data.

To find other published pSS registry reports, a comprehensive literature search in PubMed and Scopus has been done but we only found the studies using data from pSS registries. In discussion, we have used some of these studies with the biggest sample size all around the world (Tables 4 to 6). Some items which can explain observed similarities and/or discrepancies in retrieved data include the motivation of patients and physicians for participation in the disease registry and also how they are motivated for it, the pSS tracing method, type and number of pSS classification criteria which is /are used, referral rules to registry clinics which can change the percentage of patients referred by each specialty and subspecialties, the relative frequency of incident or prevalence cases, percentage of data retrieved from the hospitalized patient, using/how correctly using ICD 10 , how comorbidity was defined, care standards (for example care is based on ESSDAI recommendation or not), type of outcome measurements, subjectivity or objectivity of a data element definition (including ones related to outcome measurements), cohort type whether it is an inception cohort, a prospective or retrospective cohort and sample size. Some other additional items that can potentially explain different results are ethnicity, family support culture, weather, age distribution (relative frequency of different age groups), early versus late pSS prevalence, the composition of pSS follow-up visits/care, "it is local, national or multinational pSS registry", how much new the registry is, time lag between pSS diagnosis/classification and registry beginning, is the standardized definitions subjective or objective (more objectivity more similarity), reporting cumulative prevalence or not any type of missing data (completely at random, at random or not at random) (19).

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Table 4. Data about Region, Enrolment Criteria, Demographics and Prescribed Drugs

Country, Authors, Publication year	pSS tracing method, Sample size (#)	Including Criteria	F/M	Age at diagnosis[1]	Pred [2] (%)	DMARDs[3] (%)					
						HCQ[4]	MTX[5]	AZA[6]	LEF[7]	RITU[8]	MMF[9]
Iran, Hajiabbasi et al, 2023	Guilan Iran Primary Sjogren Registry, 74	AECG or ACR/EULAR	17.5	46.97 ± 11.93	28.3	72.97	9.46	6.76	4.05	1.35	1.35
International, Brito Zweron et al,2018	Sjogren Big Data Project, 10500	AECG	14.5	53.1 ± 14	---	---	---	---	---	---	---
International, Brito-Zweron et al, 2020	Sjogren Big Data Project, 10007	AECG	14.38	53.1 ± 14	---	---	---	---	---	---	---
International, Retamozo et al, 2019	Sjogren Big Data Project, 6331	AECG	14.15	52.3± 13.9	---	---	---	---	---	---	---
International, Retamozo et al, 2021	Sjogren Big Data Project, 12735	AECG or ACR/EULAR	14.38	52.2 ± 14.6	---	---	---	---	---	---	---
International, Maladi et al, 2012	SICCA Registry[10], 886	AECG	19	52 ± ---	---	---	---	---	---	---	---
France Seror and Gottenberg et al 2013	ASSESS Registry[11], 395	AECG	14.62	58 (51,67)	23.7	30.7	5.1	1.5	0.5	1	1.3
Sweden, Westerlund et al, 2021	ICD M35.0 at Sweden National Registries , 8884	Physician Diagnosis	≈ 9	63			28.9			0.2[12]	---
Netherlands, Borg et al, 2017	ANS cohort [13], 140	AECG	8.34	55.5 ± 14.6	---	---	---	---	---	---	---
Netherlands, Mossel et al, 2021	RESULT Cohort[14], 172	ACR/EULAR	9.75	52.9 ± 13.9	---	---	---	---	---	---	---
Spain, Chavez et al, 2018	GEAS-SS Registry[15], 1580	AECG	13.08	55.3 ± 15.4	27.9	36.39	---	---	---	3.7	---
United Kingdom, Tarn et al, 2022	UKPSS Registry[16], 931	AECG	12.89	58.1 ± 12.8	---	---	---	---	---	---	---
China D Xu et al, 2020	CRDC Registy[17], 2986	AECG or ACR/EULAR	22.8	46.31 ± 13.48	63.9	67.5	4.8	---	---	---	---
China Zung et al, 2020	CRDC Registry[17], 4087	AECG or ACR/EULAR	22.25	51.2 ± 13.1	---	---	---	---	---	---	---
China, Qian et al,2021	CRDC Registry[17], 834[18]	AECG	25.9	48.4 ± 12.7	97.4	27	---	---	---	---	---
South Korea, Lee et al,2016	KISS cohort[19], 178	AECG or ACR/EULAR	165.6	55 (47,60)	---	---	---	---	---	---	---
South Korea, Lee et al, 2018	KISS cohort[19], 328	AECG or ACR/EULAR	65.66	53 (45,59)	35.6	70.7	2.1	----	----	----	----
South Korea, Park et al, 2019	KISS cohort[19], 355	AECG or ACR	89.9	53 (43,60)	---	---	---	---	---	---	---
South Korea, Koh et al,2021	KISS cohort[19], 256	"AECG or ACR" AND 3 IgG tests[20]	61.5	55 (46,60)	36.3	68.8	3.1	2.3	---	---	---
Turkey Yazisiz et al, 2019	Diagnosed as pSS in Akdeniz University Hospital, 372	ACR	11.04	50.3 ± 11.8	33.5	90.42	28.22 (Other immunosuppressant drugs)				
Turkey Yayla et al, 2020	ICD M35.0 at Ankara University Hospital, 352	ACR/EULAR	16.54	51.6 ± 12.9	21.59	82.67	5.68	5.96	---	1.13	1.98
Turkey Aslan et al, 2022	Diagnosed as pSS in Akdeniz University Hospital, 430	ACR	11.64	58.3 ± 12.0	27.4	92			27.5 [21]		
Southern Australia, Lyne et al, 2020	SA pSS Database[22], 172	AECG and ACR./EULAR	9.1	56.8 ± 13.1	---	---	---	---	---	---	---
USA[23], Akpe et al, 2015	SICCA Registry[10], 163	AECG	10.11	51 ± 14	---	---	---	---	---	---	---
USA[23], Mathews et al, 2020	SICCA Registry[10], 126	AECG	11.65	49.7 ± 13	---	---	---	---	---	---	---

[1]. Mean ± Standard deviation, Median (25,75 inter quantile range), [2]. Prednisolon, [3]. Disease modifying antirheumatic drugs [4]. Hydroxychloroquine, [5]. Methotrexate, [6] Azathioprine, [7]. Leflunomide, [8]. Rituximab, [9]. Mycophenolate mofetile, [10]Sjogren's International Collaborative Clinical Alliance registry, [11]. Assessment of Systemic Signs and Evolution in Sjogren's Syndrome Cohort registry, [12]. Rituximab, belimumab, abatacept, tocilizumab, [13]. Antonius Nieuwegein Sjogren cohort, [14]. Registry of Sjogren Syndrome LongiTudinal (RESULT) cohort, [15].,Spanish primary Sjogren syndrome registry, [16]. United Kingdom Primary Sjogren's Syndrome Registry, [17]. Registry of Chinese patients using the Chinese Rheumatism Data Center National Disease, [18]. All have minor salivary gland biopsy, [19]. Korean Initiative Sjogren's Syndrome registry, [20]. All have three consecutive IgG tests, [21]. Azatiopürine, methotrexate, rituximab and cyclophosphamide, [22]. The South Australian (SA) primary Sjogren's Syndrome Research Clinic and Database, [23]. United States of America

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Table 5. Phenotype, Severity and Primary Sjogren Syndrome Related Quality of Life

Authors	SICCA Symptoms (%)		Organ involvement (%)												ESSDAI[1]	Disease activity severity (% DAS)			ESSPRI[2]	PASS[3] (%)
	Dry mouth	Dry eye	Constitutional	Lymphadenopathy	Glandular	Articular	Pulmonary	Hematology	Cutaneous	Renal	Muscle	PNS	CNS	Biology		Mild	Moderate	Severe		
Hajiabbasi et al	81.08	81.08	0	0	6.76	5.41	12.16	10.81	1.35	1.35	0	0	0	68.12	7.66 ± 13.96, 2 (0,6)	52.17	14.49	14.49	2.51 ± 2.28, 1.7 (1,3.33)	85.14
Brito Zweron et al (27)	93.6	92.2	10.3	9.21	22.5	38.23	10.7	25.92	11.17	5.37	2.5	6.08	1.77	58.66	6.64 ± 7.93, ---	---	---	---	---	---
Brito-Zweron et al (28)	93.7	92.4	9.5	8.6	21.4	37.7	10.4	22.4	9.4	4.4	2.3	6	1.9	51	6.1 ± 7.5, ---	38.2	29.87	11.92	---	---
Retamozo et al (30)	93.2	91.9	9.9	8.7	20.5	37	10.4	21.9	9.2	4.2	2.2	5.7	1.8	49.3	5.9 ± 7.3, ---	38.1	30.7	12	---	---
Maladi et al (31)	93	87	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Seror and Gottenberg et al (32,33)	---	---	4.1	2.4	12.1	18.6	14.4	15.6	4.2	2.8	3.3	9.6	2	37.4	----, 2 (0-7)	---	---	---	---, 5.7 (4.0,7.0)	> 50
Westerlund et al (34)	---	---	1.5	2.3	---	5.5	1.2	3.8	1.4	1.6	0.3	2.7	3.4	0.4	---	---	---	---	---	---
Mossel et al (36)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---, 4 (2,8)	43.9	41.5		6 (4.3,7)	71.8
Chavez et al (37)	97.4	96.1	---	---	---	---	---	---	---	---		---	---	---	---	---	---	---	---	---
Tarn et al (38)	---	---	---	---	---	---	---	---	---	---		---	---	---	---	---	---	---	5.4 ± 2.2, 5.7 (4,7)	---
Xu et al (39)	86.5	68.59	---	---	---	---	---	---	---	---	---	---	---	---	5.48 ± 7.2, ---	---	---	---	4.18 ± 1.85, --	Most
Zung et al (40)	89.3	79	18	9.6	15.6	25.2	20.2	18.4	9.5	6.1	3.5	4.2	1.1	34.4	---, 4 (0.9)	55.8[4]	31	13.2	---, 3.6 (2.0,5.7)	>50
Qian et al (41)	89	71.2	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Lee et al (42)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---, 3 (1,6)	---	---	---	---, 5 (4.6.3)	50
Lee et al (43)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---, 2 (0,5)	---	---	---	---, 5.3 (4,6.7)	> 50
Park et al (44)	96.3	95.8	13.6	4.8	10.7	22.9	9.6	29.1	6.5	1.1	0.8	4	0.8	54	---, 3 (1,6)	---	---	---	---, 5 (4,6)	50
Yazisiz et al (46)	99.03	98.1	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Yayla et al (19)	80.3	89.6	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Aslan et al (47)	96.04	87.9	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Lyne et al (48)	99.4	97.1	11.1	8.7	48.8	53.5	11.6	14.8	15.7	4.1	0.6	5.2	0	60.1	6.8 ± 6.07, ---	---	---	---	---	---

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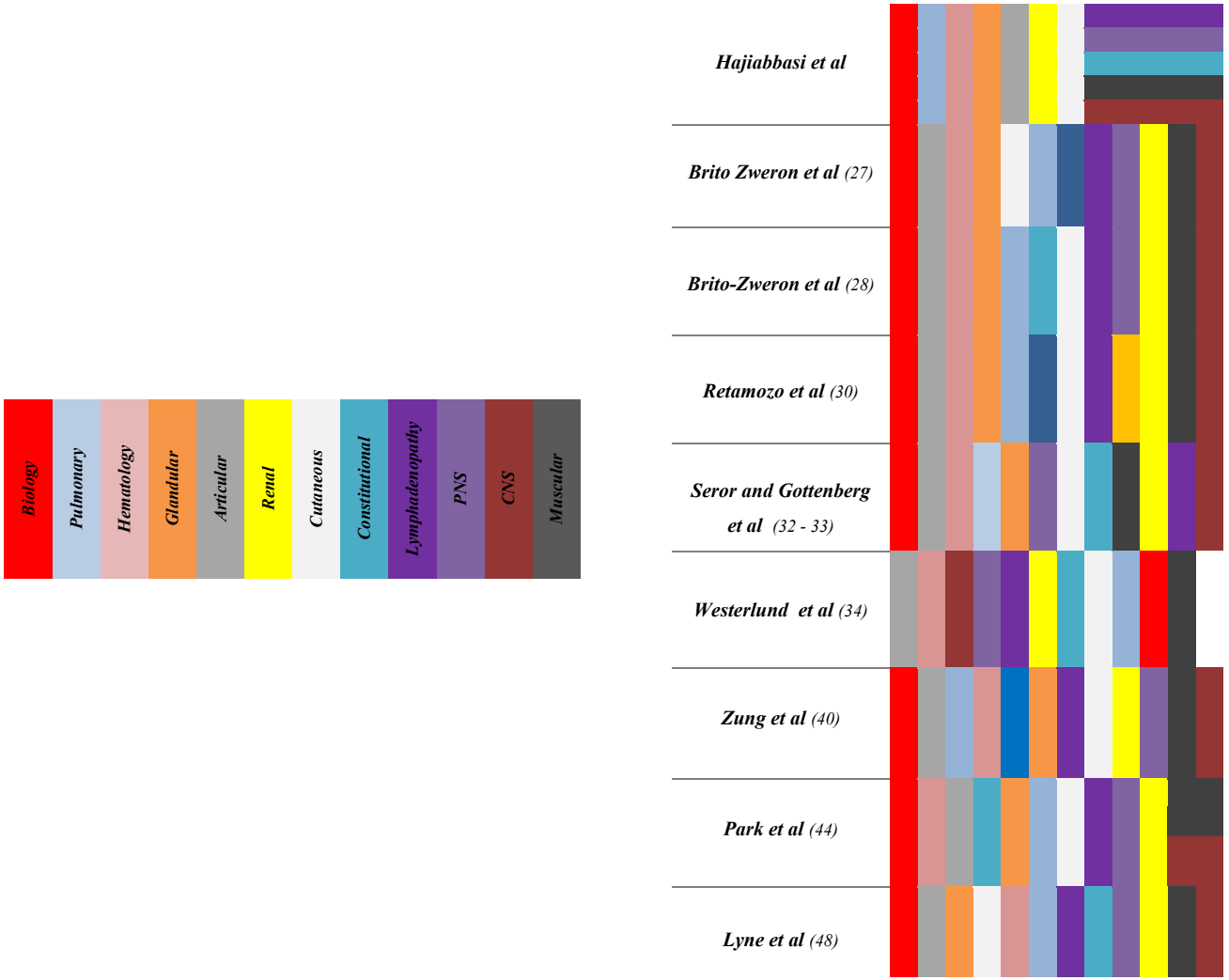

Figure 2. Organ involvement ranking (in decreasing order) in primary Sjogren syndrome registry-based studies

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Table 6. Presumptive Extra Glandular Involvement and Mortality Risk Factors of Primary Sjogren Syndrome Based on Available Evidences

Authors	Disease duration[1]	Vasculitis (%)	Parotidomegally (%)	Anti Ro+[2] (%)	Anti La +[3] (%)	RF+[4] (%)	Low C3 (%)	Low C4 (%)	Hypergammaglobulinemia (%)	High IgG (%)	Cryoglobulinemia (%)
Hajiabbasi et al	3.14 ± 4.64, 1.5 (0.2 – 4)	1.35	6.76	95.953[5]	50.46[5]	75.38[5]	16.44	2.74	50.68	12.67[6]	0
Brito Zweron et al (27)	---	---	---	73.1	45	48.5	13.4	14.4	---	---	7.2
Brito-Zweron et al (28)	---	---	---	---	---	47.9	13.4	14.6	---	---	7
Retamozo et al (30)	---	---	---	74.7	44.9	48.4	12.8	13.3	---	---	7.6
Maladi et al (31)	---	---	---	76	49	60	16	14	---	39[7]	---
Seror et al (32,33)	---, 5 (2,9)	---	---	59.2	33.5	41.1	---	19.4	---	29.3	17
Borg et al (35)	7.16 (---,---)	---	---	75	42.9	57.2	15.6	24.5	56	34.1[8]	14.3
Mossel et al (36)	---, 8 (4,13)	---	---	90.1	53.8	67.3	---	---	---	47.4	---
Chavez et al (37)	---	--	---	75.8	45.66	46.15	11.09	11.87	---	---	9.08
Tarn et al (38)	6.1 ± 5.8 .4.1 (1.7 – 8.7)	---	---	---	---	---	---	---	---	---	---
Xu et al (39)	---	3.92 (Purpura)	19.16	90.7	48.7	---	15.58	5.24	---	48.76	---
Zung et al (40)	---, 3.0 (1.0–6.0)	---	18.5	83.9	48.3	---	20.3		---	45.8	---
Qian et al (41)	---, 2.5, Range: 0,40.8	5.5 (cutaneous)	---	49.5	25.1	61.4	16.6	4.7	---	43.4[9]	---
Lee et al (42)	---, 2.12 (0.41, 4.84)	13.3 (cutaneous)	---	91		67.4	---	----	---	---	---
Lee et al (43)	---, 9.16 (0.83, 3.72)	10 (cutaneous)	---	90.2	53.6	67.4	---	---	---	---	---
Park et al (44)	---	---	--	91.8	52.5	65.9	16.4	5.1	49.7	---	3
Kohet al (45)	---, 1.2 (0.1, 4.3)	---	---	86.1	49	65.3	---	---	---	47[6]	---
Yazisiz et al (46)	6.76 ± 3.16, ---	---	----	30	16.7	32.2	---	---	37.5	---	---
Yayla et al (19)	---, 6.25 (3.7)	---	---	51.3	26.4	25.4	15.4	5.9	---	33.3	---
Aslan et al (47)	7.41±4.7, ---	---	---	48	12.7	23.1	9.2		24.2	---	---
Lyne et al (48)	---	---	---	82.6	63.2	68.9	2.4	11.8	---	---	7.5
Akpe et al (49)	---, 3 (0,13)	---	---	---	---	---	---	---	---	---	---
Mathews et al (50)	9.8, 9.6	7.1 (systemic)[10]	---	73.4	43.1	59.4	---	---	---	---	---

[1]. Mean ± Standard deviation, Median (25,75 inter quantile range). [2]. Positive Anti Ro Antibody, [3]. Positive Anti La Antibody, [4]. Positive rheumatoid factor, [5]. Positive at any time before registration, [6]. IgG >16 g/l, [7]. IgG >17.6 g/l, [8]. IgG > 18 g/l, [9]. IgG >20 g/l, [10]. 0.8% Retinal vasculitis

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Based on our experience, logically, the best including rules are ones that are compatible with current available infrastructures in a country and the best-excluding criteria are one that needs the least tests and invasive procedures for enrolling a representative sample of cases. Not meeting AECG or ACR/EULAR criteria is our exclusion criteria. Patients with pSS may have this condition for many years before diagnosis. We selected AECG criteria because both it is more specific than ACR/EULAR criteria (20) and are the only pSS criteria that can be met in pSS patients without positive SICCA symptoms or organ involvements attributable to pSS and may help us to include patients with early pSS (10). But because AECG criteria have more need for MSGB which is an invasive procedure (5) and also because it has less sensitivity in comparison to ACR/EULAR criteria (21), our other choice for excluding criteria was not meeting ACR/EULAR criteria. In addition, we don't consider ACR criteria because it is less feasible to apply than ACR/EULAR criteria (22).

In the following, we will specify our hypothetical explanation for observed similarity or discrepancy between our data and some of the highest sample size registry-based pSS studies. Hypotheses that assessing their precision degree needs more primary and secondary studies especially systematic reviews and meta-analysis studies:

- East Asia and northwest Europe had the most and the least F/M ratio (Table 1). In addition, as mentioned in the first paragraph of the discussion, more health systems utilized by women in comparison with men, especially due to cultural issues (23-26) can be potentially another explanation for this heterogeneity.

- In almost all studies, age at diagnosis was at 5-6 decades and interestingly, there was almost no heterogeneity in age decades. It comes to mind that ethnicity may be the main explanation for most observed heterogeneities.

- The mean age of GUIRAPSS patients is less than the other pSS registries (Table 4). Some explanations of this issue in the GUIRAPSS cases, as a new emerging pSS registry, could be Iran's health system composition which provides easier access of patients to the rheumatologists, high frequency of pSS cases with less than 3 years of disease duration (70.27%) (Table 6) and the less disease duration mean and median.

- Based on our knowledge, there is no comprehensive data about the ranking of prevalence of comorbidities in patients with pSS. The best data has been presented by Taren et al. through the United Kingdom Primary Sjogren Syndrome Registry (UKPSSR) (38).The other studies just determined the prevalence of some comorbidities in their samples (Table 1). In UKPSSR osteoarthritis was the most common comorbidity (36%) and the prevalence of essential hypertension (3rd most common comorbidity), hypercholesterolemia (5th most common comorbidity), fibromyalgia (8th most common comorbidity) and osteoporosis (7th most common comorbidity) were 20%, 10%, 8% and 8% respectively. In GUIRAPSS, 27.02% had at least a musculoskeletal condition (including osteoporosis). Prevalence of hypertension in the GUIRAPSS registry, China (41), UKPSSR (38) and Turkey (46) were 24.3%, 8.6%, 20% and ≈ 21.8% respectively. Prevalence of fibromyalgia in the GUIRAPSS registry, UKPSSR (38) and South Korea (45) were 10.8%, 8% and 4.7% respectively. Prevalence of DM in the GUIRAPSS registry, china (41), Turkey (46) and South Korea (45) were 8.1%, 3%, ≈ 6.3% and 3.1% respectively. Unlike GUIRAPSS, diabetes mellitus and hypothyroidism were not among the ten most common comorbidities in patients with pSS in the United Kingdom. Prevalence of hypothyroidism in patients with pSS in GUIRAPSS, China (40), Turkey (46) and South Korea (45) were 28/38%, 6.4%, 18.01% (Thyroid diseases) and 11.7% (Hashimoto thyroiditis), respectively. In spite of demonstrated differences in prevalence and rank of comorbidities in different studies, there are some similarities that may be appearing some important clues about probable most common comorbidities in patients with pSS.

- There are the evidence that pSS patients are at higher risk of cardiovascular diseases (51-53). It has been suggested that it may be due to a higher prevalence of hypertension and hypercholesterolemia in these patients, although it seems that diabetes mellitus and smoking are less prevalent in them (54). In our registered cases prevalence of hypertension is almost similar to the Iranian general population (24.32% vs 25%) but smoking (2.7% vs 13.9%) and diabetes mellitus (8.1% vs "24% for ages older than 40 years old") were less. The existence of less hypercholesterolemia ("14.8% hyperlipidemia" vs 41.6%) can be explained by our sample's younger age and higher female-to-male ratio (55-57). In addition, it has been suggested that current smoking is a protective factor for pSS (58). In all countries including Iran, the prevalence of current smokers in women is less than in men. Current smoker prevalence in Iranian women is 17% (59) and in our registered women is 1.3%. The prevalence of smoking in other studies (that is influenced by each country's culture) was between 4.3 (45) – 30% (31). Unfortunately, there was not adequate data about smoking in studies included in our discussion (Table 1).

- Owing to inadequate high-quality evidence about pSS treatment, although there are some proposed treatment guidelines, they largely developed based on expert opinions. As a result, it was not unpredictable that we observed different prevalences of drugs that have been used for the treatment of patients with pSS (Table 1). In some studies, there was no data about the relative frequency of DMARDs (conventional and biologics) and GCSs but it seems that Asian physician treatment strategies differ from European ones, especially in respect of prescribing HCQ and prednisolone. In most Asian countries prevalence of using HCQ is between 92% - 67.5% and in China prednisolone plays an important role in the treatment of patients with pSS (used 63.9% – 97.4%). However, we need more data from pSS registries, especially in regions other than Asia, for better inference.

- Dry eye and mouth prevalence increase with aging, so physicians need to correctly use their standard definitions (including the rule of pSS classification criteria) for pSS. Dry eye and dry mouth can be considered as including rule for pSS classification criteria only if:

a. For dry eye: "It be daily AND persistent AND troublesome AND for more than 3 months" OR "sensation of sand

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or gravel in patient's eye/s should occur RECURRENTLY not sometimes" OR "patients must NEED to use tear substitute 4 TIMES a day or more."

b. For dry mouth: "it must be daily AND for more than 3 months" OR "for swallowing a dry food, patients must FREQUENTLY not sometimes need to aid of liquids."

History of salivary gland enlargements can be considered as including rule for pSS classification criteria only if "patient at her/is ADULT period, not any time of life" must experience RECURRENTLY or PERSISTENTLY a swollen salivary gland that was/er NOT DUE to other etiologies."

In almost all studies, dry mouth was more common than dry eye. In addition aforementioned explanations, it may be due to longer disease duration in those studies, using or not using standard definitions of dry eye, dry mouth and salivary gland enlargements by registry teams (and how precise and accurate they used in each center), whether or not dry eye and mouth prevalence were a cumulative or not, prevalence of comorbid conditions (e.g. diabetes mellitus and mood disorders), prevalence and potency of used anticholinergic drugs and region humidity can be some other factors that can explain it. Assuming that the prevalence of dry mouth is really more than dry eye, it may be due to the fact that it is more severe, annoying and / or leading to damage than the dry eye, and as a result, patients with dry mouth are more frequently seek medical help and/or are referred to rheumatologists.

- Although there is heterogeneity in the prevalence of involved organs secondary to pSS (Table 5), this heterogeneity is less when we rank them (Figure 2). In addition to the factors mentioned in this section, some other potential causes of this heterogeneity can include:

a. As explained in the ESSDAI user guide (15), a finding must be scored in ESSDAI only if it is due to pSS AND not due to damage. For example, the ESSDAI score of renal involvement of a patient that only has a stable abnormal creatinine (for example, 3.5 mg/dl for at least 12 months) will be ZERO.

b. As we have experienced in our real-world daily practice even between expert rheumatologists (and/or other specialties or subspecialties), there is some degree of disagreement about the existence and etiology of a secondary to pSS organ involvement/s, for example, peripheral neuropathy, arthralgia, arthritis.

c. In the literature, there are some suggested organ involvement risk factors in patients with pSS that their prevalence is not similar between studies (Tables 4 and 6).

d. Not using ESSDAI for defining an organ involvement.

e. Not defined appropriate "international statistical classification of diseases and related health problems" (ICD) codes in its older version for pSS and its organ involvements. Even in ICD 10 – 2023, defined codes are not adequately matched with ESSDAI definitions for organ involvements. ESSDAI is one of the recommended core set outcome measurements for use in studies about pSS.

f. Busy clinics

g. Different quality of case report forms used in pSS registries.

- Primary Sjogren syndrome-related quality of life in our patients was high. It can be mainly explained by family support in our culture, less age (which logically is associated with more daily physical activity) (60-62), less polypharmacy score (as a proxy for drugs and conditions that can influence total dryness) (38), easy patient access to rheumatologists based on our country health system composition, care quality and fewer patients' symptom burden. Because pSS is more common in the 5^{th}- 6^{th} decades which patients at this range of life can potentially have more comorbid conditions inducing fatigue and/or pain, our rheumatologist assistant (MD) should explicitly have explained the definition of fatigue to patients and after that, she should have rechecked patient's response with a rheumatologist to be certain that patient fatigue is secondary to pSS or not? We have used the same strategy for detecting pain and its severity. We clarified for patients that they must consider the existence and severity of pain related to their pSS not osteoarthritis or other articular or muscular painful comorbid conditions. Not considering these important notes can easily change the ESSPRI score. In addition to the aforementioned notes, in our country, final decision-making about whether a pSS patient needs to other specialty or subspecialty consultation or not, is done by a rheumatologist not a GP or an internist (63). After each medical consultation, for final treatment decision-making and comprehensive patient care, patients will receive care through rheumatologist appointments. This composition of care for pSS patients may explain our lower ESSPRI score and higher PASS prevalence in comparison to other studies. On the other hand, fatigue, pain and dryness of the high symptom burden (HSB) subgroup of pSS patients respond meaningfully to HCQ (64), after finalizing the GUIRAPSS classification visit and at the time of its first activity assessment visit, 72.97% of our patients were using HCQ (70.28% more than 6 months). We have no data about the severity of fatigue, pain and dryness at the time of pSS diagnosis based on expert opinion that could guide us as to whether they were stratified as high symptom burden (HSB) pSS or not.

- Although there is a discrepancy in the prevalence of seropositivity, with respect to Anti Ro and Anti La antibodies, interestingly in almost all studies, Anti Ro Ab is positive almost twice Anti La (1.6–2).

Although at the time of using our results and proposed hypotheses about similarities and discrepancies between the GUIRAPSS and the other pSS registries data, you need to consider our limitations including:

1. At the GUIRAPSS pilot phase, based on expert rheumatologist consultations for circumventing our obstacle about the unavailability of Schirmer test strips or not doing Schirmer tests by some ophthalmologists (Because their Schirmer strips run out), we decided that (as a physician, of necessity, do in Iran clinics) in patients without the result of Schirmer test, reporting dry eye through ophthalmologist slit lamp examination was considered as positive Schirmer test. Fortunately, we have provided these strips by passengers to form abroad for our province.

2. We included patients who fulfilled either AECG or ACR/EULAR criteria, not both. Then for all cases, we did not need to do USWSFR for correct classification. But from

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now on, for gathering more comprehensive and statistically analyzable data, we have changed our protocol, and the US-WSFR test must be done for all registered patients at baseline and at each periodic classification visit (it will be done per 3 years), unless Covid 19 epidemic /pandemic recurs.

3. The absence of lissamine green dye because of Iran sanctions was another barrier to beginning the effort to establish a standardized ocular examination center (SICCA registry ocular examination sequences) that could provide an SICCA score.

4. We don't have a biobank for saliva, minor salivary glands, tears, and so on.

5. Only patients referred by rheumatologists have been accepted for registration in GUIRAPSS. This referral rule will logically change proportional to the infrastructures needed for a disease registry.

6. We opted to focus on describing GUIRAPSS and the other pSS registry data and suggesting some hypotheses for explaining observed similarities and discrepancies to prevent potentially misleading conclusions owing to a low sample size of GUIRAPSS pilot phase (increased risk of type II error). Further studies with inferential statistics are needed (when sufficient sample size is available) to assess suggested hypotheses.

As previously mentioned, because of the different sensitivity and specificity of AECG and ACR/EULAR criteria, for having a more representative sample of pSS patients in case of not fulfilled AECG criteria (When ACR/EULAR criteria have been previously met), it seems to be crucial to motivate our patients by explicitly explaining to them that AECG criteria is more specific for pSS classification. Whereby they can correctly decide whether to accept the MSGB or not.

Conclusion

Based on our knowledge, there were no comprehensive published pSS registry reports about their pilot phase (or other phases) data, as much as needed for better discussion. However, we could find baseline data of some of the oldest and biggest sample size pSS registries in published studies (or in their supplements) that have used data from these pSS registries. Based on our experience at the time of writing discussion, we noticed that there is a need for more published and more comprehensive reports about a pSS registry that will provide:

1. Brainstorming of members of different pSS registries, which can create ideas for "to the point research" (both primary and secondary ones), better care and more effective health policy making (especially resource allocation).

2. All needed data to reduce wastes in registry resources by revealing the items that are at risk of having low quality (for example, higher percentage of missing) via predefining needed risk-based approaches for these pre-specified items during a disease registry design and implementation.

3. Adequate data for precise and accurate "description about demonstrated similarities or differences" and or "statistical inferences."

Although disease registries are observational studies which for reporting them we can use the STROBE (The Strengthening the Reporting of Observational Studies in Epidemiology) guideline but it seems that developing comprehensive disease-specific standards for reporting the pSS-registry at its different phases (including defined pSS-specific disease registry quality measurement indexes) is an unmet essential need.

Authors' Contributions

All authors, as clinicians actively participating in pilot phase of the Iran Primary Sjogren Syndrome Registry (IRAPSS), contributed to data collection. Pooneh Ghavidel Parsa assessed IRAPSS data quality. Asghar Hajiabbasi and Pooneh Ghavidel Parsa collaboratively drafted the manuscript. The remining authors provided critical revisions. All authors reviewd and approved the final manuscript.

Ethical Considerations

This cohort was approved (Ethical code: IR.GUMS.REC.1398.475) at 2020-01-18 by the ethics committee of Guilan University of Medical Sciences.

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Conflict of Interests

The authors declare that they have no competing interests.

References

1. Thomas E, Hay EM, Hajeer A, Silman AJ. Sjögren's syndrome: a community-based study of prevalence and impact. Br J Rheumatol. 1998 Oct 1;37(10):1069-76.
2. Vitali C, Bombardieri S, Moutsopoulos HM, Balestrieri G, Bencivelli W, Bernstein RM, Bjerrum KB, Braga S, Coll J, Vita SD, Drosos AA. Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. Arthritis Rheum: Official Journal of the American College of Rheumatology. 1993 Mar;36(3):340-7.
3. Ng WF, Bowman SJ, Griffiths B. United Kingdom Primary Sjogren's Syndrome Registry--a united effort to tackle an orphan rheumatic disease. Rheumatology (Oxford). 2011;50(1):32-9.
4. Daniels TE, Shiboski C, Shiboski S, Lanfranchi H, Yi D, Schiødt M, Umehara H, Sugai S, Challacombe S, Greenspan JS. An early view of the international Sjögren's syndrome registry. Arthritis Rheum. 2009 May 5;61(5):711.
5. Baldini C, Talarico R, Tzioufas AG, Bombardieri S. Classification criteria for Sjogren's syndrome: a critical review. J Autoimmun. 2012;39(1-2):9-14.
6. Fox RI, Fox CM. Sjogren Syndrome: Why Do Clinical Trials Fail? Rheum Dis Clin North Am. 2016;42(3):519-30.
7. Holger Schünemann, Jan Brożek, Gordon Guyatt, and Andrew Oxman. The GRADE handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013. The GRADE working group, 2013. Available from https://gdt.gradepro.org/app/handbook/handbook.html
8. Wikipedia contributors. (2022, November 6). Gilan province. In Wikipedia, The Free Encyclopedia. Retrieved 05:16, November 16, 2022, available from https://en.wikipedia.org/w/index.php?title=Gilan_province&oldid=1120346409.
9. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjogren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Ann. Rheum. Dis.

[DOI: 10.47176/mjiri.38.134]

2017;69(1):35-45.
10. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American European Consensus Group. Ann Rheum Dis 2002;61:554–8.
11. Seror R, Theander E, Brun JG, Ramos-Casals M, Valim V, Dorner T, et al. Validation of EULAR primary Sjogren's syndrome disease activity (ESSDAI) and patient indexes (ESSPRI). Ann. Rheum. Dis 2015;74(5):859-66.
12. Vitali C, Palombi G, Baldini C, Benucci M, Bombardieri S, Covelli M, et al. Sjogren's Syndrome Disease Damage Index and disease activity index: scoring systems for the assessment of disease damage and disease activity in Sjogren's syndrome, derived from an analysis of a cohort of Italian patients. Arthritis Rheum. 2007;56(7):2223-31.
13. Seror R. Defining disease activity states and clinically meaningful improvement in primary Sjögren's syndrome with EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI). Ann Rheum Dis. 2014;0:1–8. 2016.
14. Kvien TK, Heiberg T, Hagen KB. Minimal clinically important improvement/difference (MCII/MCID) and patient acceptable symptom state (PASS): what do these concepts mean? Ann. Rheum. Dis. 2007;66 Suppl 3:iii40-1.
15. Seror R, Bowman SJ, Brito-Zeron P, Theander E, Bootsma H, Tzioufas A, Gottenberg JE, Ramos-Casals M, Dörner T, Ravaud P, Vitali C. EULAR Sjögren's syndrome disease activity index (ESSDAI): a user guide. RMD open. 2015 Feb 1;1(1):e000022.
16. John M Davism Kevin G. Moder and Gene G. Hunder. History and Physical Examination of the Musculoskeletal System. In: Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR. Kelley and Firestein's textbook of rheumatology. 12nd ed. Elsevier Health Sciences: 2021. p. 621-637.
17. Tarn JR, Howard-Tripp N, Lendrem DW, Mariette X, Saraux A, Devauchelle-Pensec V, Seror R, Skelton AJ, James K, McMeekin P, Al-Ali S. Symptom-based stratification of patients with primary Sjögren's syndrome: multi-dimensional characterisation of international observational cohorts and reanalyses of randomised clinical trials. The Lancet Rheuma. 2019 Oct 1;1(2):e85-94.
18. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.
19. Yayla ME, Karaman Z, Torgutalp M, Kelesoglu Dincer AB, Aydemir Guloksuz EG, Sezer S, et al. Early onset primary Sjogren syndrome, clinical and laboratory characteristics. Clin. Rheumatol. 2020;39(9):2689-96.
20. Le Goff M, Cornec D, Jousse-Joulin S, Guellec D, Costa S, Marhadour T, et al. Comparison of 2002 AECG and 2016 ACR/EULAR classification criteria and added value of salivary gland ultrasonography in a patient cohort with suspected primary Sjogren's syndrome. Arthritis Res Ther. 2017;19(1):269.
21. Tsuboi H, Hagiwara S, Asashima H, Takahashi H, Hirota T, Noma H, et al. Comparison of performance of the 2016 ACR-EULAR classification criteria for primary Sjogren's syndrome with other sets of criteria in Japanese patients. Ann Rheum Dis. 2017;76(12):1980-5.
22. Hernandez-Molina G, Avila-Casado C, Nunez-Alvarez C, Cardenas-Velazquez F, Hernandez-Hernandez C, Luisa Calderillo M, et al. Utility of the American-European Consensus Group and American College of Rheumatology Classification Criteria for Sjogren's syndrome in patients with systemic autoimmune diseases in the clinical setting. Rheumatology (Oxford). 2015;54(3):441-8.
23. Redondo-Sendino A, Guallar-Castillon P, Banegas JR, Rodriguez-Artalejo F. Gender differences in the utilization of health-care services among the older adult population of Spain. BMC public health. 2006;6:155.
24. Noh JW, Kim KB, Park H, Kwon YD. Gender Differences in Outpatient Utilization: A Pooled Analysis of Data from the Korea Health Panel. J Womens Health (Larchmt). 2017;26(2):178-85.
25. Gajovic G, Janicijevic K, Andric D, Djurovic O, Radevic S. Gender Differences in Health Care Utilization Among the Elderly. Serb. J. Exp. Clin. Res. 2021;22(3):195-203.
26. Wang Y, Hunt K, Nazareth I, Freemantle N, Petersen I. Do men consult less than women? An analysis of routinely collected UK general practice data. BMJ open. 2013;3(8):e003320.
27. Retamozo S, Acar-Denizli N, Ng WF, Rasmussen A, Mandl T, Seror R, Li X, Baldini C, Gottenberg JE, Danda D, Quartuccio L. How immunological profile drives clinical phenotype of primary Sjögren's syndrome at diagnosis: analysis of 10.500 patients (Sjögren Big data project. InACR/ARHP Annual Meeting 2018 Oct 19 (Vol. 70, No. Abstrat 2881, p. 3234).
28. Brito-Zeron P, Acar-Denizli N, Ng WF, Horvath IF, Rasmussen A, Seror R, et al. Epidemiological profile and north-south gradient driving baseline systemic involvement of primary Sjogren's syndrome. Rheumatology (Oxford). 2020;59(9):2350-9.
29. Retamozo, S., Acar-Denizli, N., Rasmussen, A., Horvath, I.F., Baldini, C., Priori, R., Sandhya, P., Hernandez-Molina, G., Armagan, B., Praprotnik, S. and Kvarnstrom, M., 2019. Systemic manifestations of primary Sjögren's syndrome out of the ESSDAI classification: prevalence and clinical relevance in a large international, multi-ethnic cohort of patients. Clin Exp Rheumatol, 37(3 (S118)), pp.97-106.
30. Retamozo S, Acar-Denizli N, Horváth IF, Ng WF, Rasmussen A, Dong X, Li X, Baldini C, Olsson P, Priori R, Seror R. Influence of the age at diagnosis in the disease expression of primary Sjögren syndrome. Analysis of 12,753 patients from the Sjögren Big Data Consortium. Clin Exp Rheumatol. 2021;39(6):S166-74.
31. Malladi AS, Sack KE, Shiboski SC, Shiboski CH, Baer AN, Banushree R, et al. Primary Sjögren's syndrome as a systemic disease: a study of participants enrolled in an international Sjögren's syndrome registry. Arthritis care & research. 2012;64(6):911-8
32. Seror R, Gottenberg JE, Devauchelle-Pensec V, Dubost JJ, Le Guern V, Hayem G, et al. European League Against Rheumatism Sjogren's Syndrome Disease Activity Index and European League Against Rheumatism Sjogren's Syndrome Patient-Reported Index: a complete picture of primary Sjogren's syndrome patients. Arthritis care & research. 2013;65(8):1358-64.
33. Gottenberg JE, Seror R, Miceli-Richard C, Benessiano J, Devauchelle-Pensec V, Dieude P, et al. Serum levels of beta2-microglobulin and free light chains of immunoglobulins are associated with systemic disease activity in primary Sjogren's syndrome. Data at enrollment in the prospective ASSESS cohort. PloS one. 2013;8(5):e59868.
34. Westerlund A, Kejs AMT, Beydogan H, Gairy K. Primary Sjogren's Syndrome: A Retrospective Cohort Study of Burden of Illness in Sweden. Rheumatol Ther. 2021;8(2):955-71.
35. Ter Borg EJ, Kelder JC. Development of new extra-glandular manifestations or associated auto-immune diseases after establishing the diagnosis of primary Sjogren's syndrome : A long-term study of the Antonius Nieuwegein Sjogren (ANS) cohort. Rheumatol Int. 2017;37(7):1153-8
36. Mossel E, van Nimwegen JF, Stel AJ, Wijnsma RF, Delli K, van Zuiden GS, Olie L, Vehof J, Los LI, Vissink A, Kroese FG. Clinical phenotyping of primary Sjögren syndrome patients using salivary gland ultrasonography: data from the result cohort. J Rheumatol. 2021 May 1;48(5):717-27.
37. Flores-Chávez A, Kostov B, Solans R, Fraile G, Maure B, Feijoo-Massó C, 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(3):121-9.
38. Tarn J, Lendrem D, Barnes M, Casement J, Ng WF. Comorbidities in the UK Primary Sjögren's Syndrome Registry. Front Immunol. 2022 Apr 22;13:864448.
39. Xu D, Zhao S, Li Q, Wang YH, Zhao JL, Li MT, Zhao Y, Zeng XF. Characteristics of Chinese patients with primary Sjögren's syndrome: preliminary report of a multi-centre registration study. Lupus. 2020 Jan;29(1):45-51.
40. Zhang Y, Li M, Zhang L, Li Q, Yang P, Kong X, et al. Association between comorbidities and extraglandular manifestations in primary Sjogren's syndrome: a multicenter cross-sectional study. Clin Rheumatol. 2020;39(9):2677-88.
41. Qian J, He C, Li Y, Peng L, Yang Y, Xu D, Fei Y, Zhang W, Zhao Y, Dong Y, Li Y. Ten-year survival analysis of patients with primary Sjögren's syndrome in China: a national prospective cohort study. Ther Adv Musculoskelet Dis. 2021 Jun;13:1759720X211020179.
42. Cho HJ, Yoo JJ, Yun CY, Kang EH, Lee HJ, Hyon JY, Song YW, Lee YJ. The EULAR Sjögren's syndrome patient reported index as an independent determinant of health-related quality of life in primary Sjögren's syndrome patients: in comparison with non-Sjögren's sicca patients. Rheumatology (Oxford). 2013 Dec 1;52(12):2208-17.
43. Lee J, Koh JH, Kim JW, Sung YK, Lee SS, Choe JY, et al. Performance of the 2016 ACR-EULAR classification criteria for primary Sjogren's syndrome in a Korean cohort. Rheumatol Int.

[DOI: 10.47176/mjiri.38.134]

2018;38(9):1651-60.
44. Park Y, Lee J, Koh JH, Sung YK, Lee SS, Choe JY, Shim SC, Kim JM, Kwon SR, Kim HO, Chung SH. Distinct clinical characteristics of anti-Ro/SSA-negative primary Sjögren's syndrome: data from a nationwide cohort for Sjögren's syndrome in Korea. Clin Exp Rheumatol. 2019 May 1;37(Suppl 118):107-13.
45. Koh JH, Park Y, Lee J, Park SH, Kwok SK. Hypergammaglobulinaemia predicts glandular and extra-glandular damage in primary Sjögren's syndrome: results from the KISS cohort study. Clin Exp Rheumatol. 2021 Jan 1;39(6):114-22.
46. Yazisiz V, Göçer M, Erbasan F, Uçar İ, Aslan B, Oygen Ş, Gökalp Gök E, Terzioğlu ME. Survival analysis of patients with Sjögren's syndrome in Turkey: a tertiary hospital-based study. Clin Rheumatol. 2020 Jan;39:233-41.
47. Aslan B, Ogut TS, Erbasan F, Dilbil M, Celik E, Terzioglu ME, et al. The risk of cancer in patients with primary Sjogren syndrome: a single-center study from Turkey. Turk J Med Sci. 2022;52(3):587-95
48. Lyne SA, Downie-Doyle S, Lester SE, Quinlivan A, Toby Coates P, Gordon TP, Rischmueller M. Primary Sjögren's syndrome in South Australia. Clin Exp Rheumatol. 2020 Jan 1;38(126):S57-63.
49. Akpek EK, Mathews P, Hahn S, Hessen M, Kim J, Grader-Beck T, et al. Ocular and systemic morbidity in a longitudinal cohort of Sjogren's syndrome. Ophthalmology. 2015;122(1):56-61.
50. Mathews PM, Robinson SA, Gire A, Baer AN, Akpek EK. Extraglandular ocular involvement and morbidity and mortality in primary Sjogren's Syndrome. PloS one. 2020;15(9):e0239769.
51. Brito-Zerón P, Flores-Chávez A, Horváth IF, Rasmussen A, Li X, Olsson P, Vissink A, Priori R, Armagan B, Hernandez-Molina G, Praprotnik S. Mortality risk factors in primary Sjögren syndrome: a real-world, retrospective, cohort study. EClinicalMedicine. 2023 Jul 1;61.
52. Beltai A, Barnetche T, Daien C, Lukas C, Gaujoux-Viala C, Combe B, et al. Cardiovascular Morbidity and Mortality in Primary Sjogren's Syndrome: A Systematic Review and Meta-Analysis. Arthritis Care Res (Hoboken). 2020;72(1):131-9.
53. Yong WC, Sanguankeo A, Upala S. Association between primary Sjögren's syndrome, cardiovascular and cerebrovascular disease: a systematic review and meta-analysis. Clin Exp Rheumatol. 2018 Mar 19;36(Suppl 112):190-7.
54. E. William S. Clair, David L. Sjogren Syndrome. In: Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR. Kelley and Firestein's textbook of rheumatology. 12nd ed. Elsevier Health Sciences: 2021. p. 1284- 1306.
55. Haghdoost AA, Rezazadeh Kermani M, Sadghirad B, Baradaran HR. Prevalence of type 2 diabetes in the Islamic Republic of Iran: systematic review and meta-analysis. East Mediterr Health J. 2009;15 (3), 591-599.
56. Oori MJ, Mohammadi F, Norozi K, Fallahi-Khoshknab M, Ebadi A, Gheshlagh RG. Prevalence of HTN in Iran: Meta-analysis of Published Studies in 2004-2018. Curr Hypertens Rev. 2019;15(2):113-22.
57. Tabatabaei-Malazy O, Qorbani M, Samavat T, Sharifi F, Larijani B, Fakhrzadeh H. Prevalence of dyslipidemia in Iran: a systematic review and meta-analysis study. Int J Prev Med. 2014 Apr;5(4):373.
58. Gebreegziabher EA, Oldenburg CE, Shiboski SC, Baer AN, Jordan RC, Rose-Nussbaumer JR, Bunya VY, Akpek EK, Criswell LA, Shiboski CH, Lietman TM. Associations between smoking and primary Sjögren syndrome classification using the Sjögren's international collaborative clinical alliance cohort. ACR Open Rheumatol. 2022 Mar;4(3):231-7.
59. Jafari A, Rajabi A, Gholian-Aval M, Peyman N, Mahdizadeh M, Tehrani H. National, regional, and global prevalence of cigarette smoking among women/females in the general population: a systematic review and meta-analysis. Environ Health Prev Med. 2021;26(1):5
60. Pertovaara M, Korpela M. Regular physical activity is associated with lower levels of ESSPRI and other favourable patient-reported outcomes in patients with primary Sjögren's syndrome. Clin Exp Rheumatol 2016;34(3):560.
61. Wouters EJ, van Leeuwen N, Bossema ER, Kruize AA, Bootsma H, Bijlsma JW, et al. Physical activity and physical activity cognitions are potential factors maintaining fatigue in patients with primary Sjogren's syndrome. Ann Rheum Dis. 2012;71(5):668-73.
62. Strömbeck BE, Theander E, Jacobsson LT. Effects of exercise on aerobic capacity and fatigue in women with primary Sjögren's syndrome. Rheumatology (Oxford). 2007 May 1;46(5):868-71.
63. Seghieri C, Lupi E, Tzioufas AG, De Vita S, Baldini C. Patient-reported experience and health-related quality of life in patients with primary Sjögren's syndrome in Europe. Am J Ophthalmol. 2021 Jan 1;39(6):123-30.
64. Collins A, Lendrem D, Wason J, Tarn J, Howard-Tripp N, Bodewes I, Versnel MA, Gottenberg JE, Seror R, Mariette X, Ng WF. Revisiting the JOQUER trial: stratification of primary Sjögren's syndrome and the clinical and interferon response to hydroxychloroquine. Rheumatol Int. 2021 Sep;41(9):1593-600.

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