PORTRESS – the PORTuguese Reuma.pt registry for Sjögren'S disease

Bandeira M[1,2*], Silvério-António M[1,2], Pereira da Costa R[1,2], Lopes AR[1,2], Cunha-Santos F[3], Pereira PJ[4], Belchior Raimundo D[5], Cunha A[6], Pinto Oliveira C[7], Duarte AC[8], Dias J[9], Emília Santos M[10], Gonçalves MJ[10,11,12], Moniz AC[10], Maduro AI[13], Luís M[13], Valido A[14], Oliveira M[15], Brites L[16], Tenazinha C[17], Vieira A[18], Khmelinskii N[1,2], Barcelos F[19,20], Fonseca JE[1,2], Romão VC[1,2], *PORTRESS Reuma.pt Task Force*

PORTRESS Reuma.pt Task Force: Silva M[2], Paiva Dinis S[3], Vinagre F[21], Lourenço MH[10], Bento Silva A[10], Daniel A[16], Valente P[22], Almeida I[23], Pontes Ferreira M[6], Silva-Dinis J[24], Costa C[25], Teixeira L[26], Araújo F[27], Marques Gomes C[28], Pinto P[29], Farinha F[30], Nóvoa T[31], Rodrigues A[32], Cortes S[33]

1 Serviço de Reumatologia, Unidade Local de Saúde Santa Maria, Centro Académico de Medicina de Lisboa (CAML), Lisboa, Portugal;
2 Gulbenkian Institute for Molecular Medicine, Faculdade de Medicina, Universidade de Lisboa, CAML, Lisboa, Portugal;
3 Serviço de Reumatologia, Unidade Local de Saúde da Guarda, Guarda, Portugal;
4 Serviço de Reumatologia, Unidade Local de Saúde de Braga, Braga, Portugal;
5 Serviço de Reumatologia, Unidade Local de Saúde Loures-Odivelas, Loures, Portugal
6 Serviço de Reumatologia, Unidade Local de Saúde do Alto Minho, Ponte de Lima, Portugal;
7 Serviço de Reumatologia, Unidade Local de Saúde da Região de Aveiro, Aveiro, Portugal;
8 Serviço de Reumatologia, Unidade Local de Saúde Almada-Seixal, Almada, Portugal;
9 Serviço de Reumatologia, Unidade Local de Saúde Médio Tejo, Torres Novas, Portugal
10 Serviço de Reumatologia, Unidade Local de Saúde Lisboa Ocidental, Lisboa, Portugal;
11 Serviço de Reumatologia, Hospital CUF Santarém, Santarém, Portugal;
12 Instituto Politécnico de Lisboa, Escola Superior de Tecnologia da Saúde de Lisboa, Lisboa, Portugal
13 Serviço de Reumatologia, Unidade Local de Saúde de Coimbra, Coimbra, Portugal;
14 Serviço de Reumatologia, Unidade Local de Saúde do Litoral Alentejano, Santiago do Cacém, Portugal.
15 Serviço de Reumatologia, Unidade Local de Saúde da Cova da Beira, Covilhã, Portugal;
16 Serviço de Reumatologia, Unidade Local de Saúde da Região de Leiria, Leiria, Portugal;
17 Serviço de Reumatologia, Unidade Local de Saúde do Algarve, Faro, Portugal;
18 Sjögren's Disease Patient Representative, Sjögren's Europe
19 Serviço de Reumatologia, Hospital CUF Descobertas, Lisboa, Portugal;
20 Instituto Português de Reumatologia, Lisboa, Portugal;
21 Hospital da Luz, Setúbal, Portugal
22 Serviço de Reumatologia, Unidade Local de Saúde de Entre Douro e Vouga, Santa Maria da Feira, Portugal;
23 Unidade de Reumatologia, Unidade Local de Saúde Dão-Lafões, Viseu, Portugal;
24 Unidade de Reumatologia, Unidade Local de Saúde São José, Lisboa, Portugal.;
25 Serviço de Reumatologia, Unidade Local de Saúde Trás-os-Montes e Alto Douro, Vila Real, Portugal;

[26] Serviço de Reumatologia, Hospital Dr. Nélio Mendonça, Hospital Central do Funchal, Funchal, Portugal;
[27] Serviço de Reumatologia, Hospital CUF Cascais, Cascais, Portugal;
[28] Serviço de Reumatologia, Unidade Local de Saúde de São João, Porto, Portugal;
[29] Serviço de Reumatologia, Unidade Local de Saúde de Gaia e Espinho, Vila Nova de Gaia, Portugal;
[30] Unidade de Reumatologia, Unidade Local de Saúde da Lezíria, Santarém, Portugal;
[31] Serviço de Reumatologia, Unidade Local de Saúde da Ilha de São Miguel, Hospital Divino Espírito Santo, Ponta Delgada, Portugal
[32] Serviço de Reumatologia, Hospital do Santo Espírito da Ilha Terceira, Angra do Heroísmo, Portugal
[33] Quadrantes - Clínica de Cascais, Cascais, Portugal

* ORCID: 0000-0001-8312-4532

Short title: PORTRESS – the PORTuguese Reuma.pt registry for Sjögren'S disease

Correspondence to

Matilde Bandeira

E-mail: matilde.bandeira@ulssm.min-saude.pt

Submitted: 27/01/2025

Accepted: 16/06/2025

Abstract

Aims: Sjögren's disease (SjD) is a complex disease with a wide variety of manifestations and outcomes. We recently created PORTRESS, the Portuguese SjD registry within Reuma.pt. We aim to describe this registry and characterize our national cohort.

Methods: We included patients with a clinical diagnosis of SjD, registered in PORTRESS up to November 2023. Demographic, clinical, treatment, and patient-reported outcomes (PROs) data were collected. Variables were compared according to parametric or non-parametric tests, as applicable.

Results: A total of 1375 patients were included. Patients fulfilled AECG 2002 or ACR/EULAR 2016 classification criteria in 62% and 57% of cases, respectively, although more than half didn't have a complete assessment of all items. Of note, the vast majority (93%) had both SjD manifestations and a positive anti-Ro and/or minor salivary gland biopsy.

Most patients (88%) exhibited at least one active ESSDAI domain during the course of their disease. Hydroxychloroquine and corticosteroids were used in 52% and 30% of patients, while other immunosuppressants and pilocarpine in 12% and 18% of cases, respectively.

The mean ESSDAI at inclusion was 3.0±4.4 (range 0-42), and, at the last follow-up, 2.1±3.7 (0-31), corresponding to a significant decrease. Dryness, pain and fatigue PROs were scored high, with a significant increase from baseline to follow-up.

Conclusion: PORTRESS is a web-based SjD registry facilitating efficient nationwide data storage. It enables research, trial recruitment, and a comprehensive longitudinal view of patients' evolution. Although systemic activity improved over follow-up, symptom burden worsened when compared to baseline, underlining a major unmet need in SjD.

Keywords: bDMARDs; Disease activity; Quality of health care; Sjogren's syndrome; DMARDs; Epidemiology

Key messages

- PORTRESS is the first nationwide registry providing comprehensive insights into Sjögren's disease (SjD) management in Portugal.
- A significant part of real-world SjD patients lack complete classification criteria data, excluding them from many studies and clinical trials.
- This study highlights unmet needs in SjD, including persistent symptom burden despite improved systemic activity.

Introduction

Sjogren's disease (SjD) is a systemic immune-mediated disorder that may present with several clinical manifestations[1]. For the last couple of decades it has become more evident just how complex SjD truly is, with a wide variety of possible multiorgan involvement[2,3]. A multifaceted patient evaluation is, therefore, fundamental. Registries allow for a more complete data collection, providing a clearer depiction of patients followed in the "real world". They are, thus, key in supporting research on this disease[4–7]. Easy-to-complete electronical medical records may aid systematic patient assessment in everyday clinical practice and help harmonise data collection for subsequent analysis.

Reuma.pt, the Rheumatic Diseases Portuguese Register, was created in 2008 and is a web-based registry aimed at supporting routine clinical practice[8]. It currently includes 15 different modules, 13 for specific diseases (SjD, myositis, vasculitis, systemic lupus erythematosus (SLE), systemic sclerosis, spondylarthritis, psoriatic arthritis, rheumatoid arthritis, early arthritis, juvenile idiopathic arthritis, autoinflammatory syndromes, osteoarthritis, and osteoporosis) and two for miscellaneous adult or paediatric diagnoses. There are currently over 35,000 registered patients from 74 centres in Portugal, with over 300,000 visits[9]. During 2023, more than 4,000 new patients and 30,000 new visits were recorded, reinforcing a continuous and sustainable growth of this registry[9].

Recently, a specific module within Reuma.pt for SjD was created, building the basis for the PORTtuguese REgistry of Sjögren'S disease — PORTRESS. Our aim is to describe the structure of PORTRESS and briefly characterize the patients registered since its creation.

Methods

Description of the module

Reuma.pt is a web-based medical record that allows for the prospective collection and storage of data. Patients are required to sign a specific informed consent for data registration and use in research. All data is encrypted and only accessible by the clinicians of each centre. This registry has been approved by all the ethics committees of member institutions and also the Portuguese Data Protection National Commission[8]. Different modules for each disease have been developed, some of which have been previously described[10,11].

For each appointment, data may be collected on a variety of fields, which are outlined in the left-hand side of the website (Figure 1). These fields include standard data that are common to all disease modules and also more detailed SjD-specific data.

Standard data include patient identification, informed consent (status, date and uploaded file), demographics (date of birth, ethnicity, and marital, education and working statuses), date of symptom onset, date of diagnosis, comorbidities (including previous surgeries), smoking and alcohol habits, past and ongoing medication, vaccines, tuberculosis screening, and quality-of-life assessments (short form 36 [SF36], EuroQol-5D [EQ-5D], functional assessment of chronic illness therapy [FACIT] fatigue scale, and hospital anxiety and depression scale [HADS]). In addition, there is a section on adverse events which is electronically linked to the National Authority of Medicines and Health Products – INFARMED.

Reuma.pt is also accessible by the patients, who have a personalized password and their own dedicated area to access online and fill out patient reported outcomes (PROs) before each appointment.

The module for SjD, PORTRESS, is aimed at all patients with a clinical diagnosis of SjD (i.e., in the opinion of the attending physician). It collects disease-specific data that is divided into “general data” and “current appointment”. The former includes all the characteristics of SjD for a given patient, including date of symptom onset and diagnosis; presence and onset date of dryness, fatigue, pain; and diagnostic certainty (SjD, “associated” SjD, sicca non-Sjögren and undifferentiated connective tissue disease; fairly certain to unlikely). There is an area for classification criteria, including both the 2002 American European Consensus Group (AECG) and the 2016 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) criteria. The 2012 ACR-SICCA criteria were originally included but later moved to a secondary menu. Data completion using information from other sections and classification criteria fulfilment assessment is performed automatically.

PORTRESS also allows for a multidisciplinary evaluation of the patient. Specifically, there are sections dedicated to Ophthalmologists and Oral Medicine/Dentistry specialists, who also have access to the patient’s electronic file. In these sections, there are several fields including all oral and ocular tests incorporated in the classification criteria, such as salivary flow (unstimulated/stimulated), ocular staining score (OSS), van Bijsterveld score (vBS), and Schirmer’s test. An abnormal result in each of these tests is automatically flagged. In addition, complete ocular and oral examinations as well as specific PROs such as Symptom Assessment in Dry Eye (SANDE) and ocular surface disease index (OSDI) are also available.

Other relevant sections are dedicated to multiorgan involvement and lymphoma risk factors. The former displays all EULAR Sjögren’s Syndrome Disease Activity Index (ESSDAI) domains, as well as gastrointestinal/hepatobiliary and ‘other’ involvements. Each domain is assessed according to the ESSDAI definition and can be marked as 'yes/no/not available', together with a date, and additional observations. The other section lists known risk factors for lymphoma

development, including persistent salivary gland swelling, lymphadenopathy, purpura or ectopic lymphoid structures in salivary gland biopsy.

A section on 'Salivary gland evaluation' allows the reporting of minor salivary gland biopsy (including Chisholm-Mason score and an automatic focus score calculator), major salivary gland ultrasound (including EULAR-Outcome Measures in Rheumatology [EULAR-OMERACT] score) and salivary gland scintigraphy (including Schall scale).

Furthermore, there is an 'immunologic profile' section that contains data on autoantibodies (ANA, anti-SSA/Ro (Ro-52 and Ro-60), anti-SSB/La, rheumatoid factor, anti-cyclic citrullinated peptides, antiphospholipid), cryoglobulins, hypergammaglobulinemia, immunoglobulin G levels and monoclonal gammopathy.

A key aspect of PORTRESS is its incorporation of key outcome measures for disease activity (e.g., ESSDAI), impact (e.g., EULAR Sjögren's Syndrome Patient Reported Index [ESSPRI], and EULAR Sicca Score [ESS]) and damage (e.g., Sjögren's Syndrome Damage Index [SSDI], and Sjögren's Syndrome Disease Damage Index [SSDDI]). All of these tools can be filled in during a consultation and a final score is automatically calculated. Of note, ESSDAI includes notes on the definition of each domain involvement and severity degree, which aids clinicians in accurately assessing systemic disease. If there is active joint involvement, tender and swollen joint counts can be registered in a homunculus, together with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values. Other PROs less often used in daily practice are also available, including the SjD-targeted Profile of Fatigue and Discomfort – Sicca Symptoms Inventory (PROFAD-SSI), and general quality of life questionnaires such as the Health Assessment Questionnaire (HAQ), EQ-5D, HADS, SF36, and FACIT.

Another important feature of Reuma.pt is that it allows patients registered in other modules (e.g., SLE), who also have SjD, to have the same specific disease assessment tools available. This enables the evaluation of these patients in a detailed manner, as described for PORTRESS.

Patient recruitment, inclusion criteria and implementation

We performed a multicentre retrospective longitudinal study based on PORTRESS and included patients according to the following inclusion criteria: (i) clinical diagnosis of SjD by the assisting rheumatologist; (ii) registered in PORTRESS; (iii) at least one registered clinical evaluation. Patients with overlap syndromes, e.g., fulfilling classification criteria for both SjD and another inflammatory rheumatic and musculoskeletal disease (RMD) could be included. On the contrary, patients with another RMD who only had sicca features but no other findings suggestive of SjD (e.g., positive salivary gland biopsy, anti-Ro, Schirmer's) were not included.

All Rheumatology centres in Portugal that work with Reuma.pt are allowed to register patients in PORTRESS. For this study, each centre was invited to participate and actively include SjD patients with full clinical information.

Statistical analysis

Data from all patients included up to November 2023 were obtained. Demographic, clinical, treatment and PROs data were collected. Variables were compared according to parametric or non-parametric tests, as applicable.

Descriptive statistics were presented as mean ± standard deviation for continuous variables, and as absolute and relative frequencies (%) for categorical variables.

Frequencies of categorical variables were compared using Chi-square or Fisher's test, whereas continuous variables were compared using Student's t-Test or Mann-Whitney Test, as appropriate (according to normality and variance homogeneity).

Variation of disease activity (ESSDAI) and impact (ESSPRI) scores at baseline and end of follow-up were calculated using Paired T-test or Wilcoxon Sign Rank Test, as appropriate. Statistical significance was set at $p < 0.05$ and statistical analyses were performed using SPSS.

Ethical considerations

The study was conducted according to the principles of the Declaration of Helsinki (revised in Fortaleza – 2013) and was approved both by the Ethics Committee of *Centro Académico de Medicina de Lisboa* (CAML – 169/22) and the Reuma.pt National Committee. Included patients signed a specific informed consent for Reuma.pt, allowing the registration of data and its use for research. All data were pseudo anonymised and exported by the Reuma.pt management team.

Results

Demographic data

1375 patients with SjD were included (Table I), 95% of whom were females, with a mean age of 61.8±14.4 years. Patients were included from 31 different Rheumatology centres, with one centre that has a dedicated multidisciplinary clinic for SjD having recruited 470 patients (34%). Most included patients were Caucasian (93%), 5% of African ancestry and 1% Asian. The majority of patients had never smoked (78%), 14% were past smokers, and 8% were current smokers. The mean age at diagnosis and symptom onset was 52.7±14.7 and 47.9±14.8 years, respectively,

with a diagnosis delay of 4.6±5.9 years. The mean time of total follow-up was 13.2±8.9 years, and the time of follow-up after inclusion in the SjD-specific module was 4.29±2.49 years.

Symptoms and systemic involvement

Regarding the most commonly reported symptoms in SjD, 74% of our patients (n=1008/1370) reported xerostomia, 70% (n=956/1367) xeropthalmia, 51% (n=677/1330) reported musculoskeletal pain, and 40% (n=511/1283) complained of troublesome fatigue. Dryness of additional surfaces such as vaginal or skin dryness was reported by 21% of patients (n=232/1107).

Most patients (88%) had at least one active ESSDAI domain over the course of the disease. Systemic involvement was observed in various forms among patients, and affected most commonly the biologic (52%), articular (43%), hematologic (35%), and glandular (31%) domains. Constitutional and cutaneous involvements were each observed in roughly one fifth (18%) of the patients, whereas other less frequently affected domains included lymphadenopathic (11%), pulmonary (9%), peripheral nervous system (4%), renal (3%), gastrointestinal/hepatobiliary (3%), muscular (2%), and central nervous system (2%) domains. Excluding biological and haematological activity, both of which poorly correlate with disease impact, systemic involvement was still observed in almost two thirds of patients (64%). Of note, considering all systems accounted for in ESSDAI, 63% of patients had more than one ESSDAI domain involved during the disease course (n=757/1204, 38% of whom with ≥3 domains), with a median (IQR) number of domains involved of 2 (2).

Autoantibodies, salivary gland biopsy/ultrasound and other diagnostic tests

Most patients were positive for ANA (91%) and anti-SSA/Ro (82%) and almost half had circulating rheumatoid factor. Anti-Ro-52 and anti-Ro-60 antibodies were not available in many centres, but were observed in 87% (n=454/522) and 92% (n=516/563) of patients, respectively, while anti-SSB/La antibodies were less prevalent (45%, n=541/1204). Hypergammaglobulinemia (49%) and raised immunoglobulin G (40%) were common, unlike cryoglobulinemia (8%), which was reported in only 61% of patients (n=835/1375).

Two thirds of patients had an available minor salivary gland biopsy (n=918/1375, 67%), 53% of whom had a Chisholm-Mason Grade ≥3. Mild or no changes were observed in 30% of patients (Grades 0/1), while 17% had moderate lymphocytic infiltration with a focus score ≤1 (Grade 2). The numeric value of the focus score was available in 29% of patients (n=265/918), with a mean of 1.6±2.1.

Regarding exocrine glandular function, Schirmer's test was reduced in 59% of patients, whereas only 22% had an unstimulated whole salivary flow below the threshold of 0.1ml/min (as defined in SjD classification criteria). The proportion of patients with a positive keratoconjunctivitis sicca (KCS) score was even lower at 13% (based on standard OSS/vBS criteria). Of note, the number of patients with full assessment of lacrimal (n=972/1375, 71%) and salivary flow (n=719/1375, 52%) and KCS (n=672/1375, 49%) was low among the cohort.

At least one known risk factor for lymphoma from the list within Reuma.pt (Figure 1) was present in a significant part of the cohort (n=579/1158, 49%). Lymphopenia (23%) and low C3 (18%) were the most common, followed by decreased C4 (9%) and persistent salivary gland swelling (8%). Cryoglobulins (8%), cutaneous vasculitis (6%), and monoclonal gammopathy (6%) were less frequently present.

Classification criteria

Patients fulfilled AECG 2002 or ACR/EULAR 2016 classification criteria in 62% and 57% of cases, respectively. A slightly higher proportion (63%) fulfilled at least one of these set of criteria. However, a large percentage of patients (n=769/1375, 56%) did not have a complete assessment of all criteria in daily clinical practice (Supplementary Table I). In fact, 49% had only 3 or less of the 5 items included in the ACR/EULAR 2016 criteria set. Importantly, however, the vast majority of patients had both sicca symptoms (or ESSDAI-defined extraglandular involvement) and a positive anti-SSA/Ro and/or minor salivary gland biopsy (n=1130/1210, 93%).

Disease activity, impact and treatment

The mean ESSDAI at inclusion was 3.0±4.4 (range 0-42), corresponding to 77% (n=800/1039) of patients with low systemic disease activity (ESSDAI<5; Figure 2). At the last follow-up visit, the mean ESSDAI was 2.1±3.7 (range 0-31), corresponding to a significant decrease from baseline (Figure 3-A). Around 24% of patients experienced worsening disease activity, whereas 46% showed improvement (Figure 3-B).

Symptom burden, as assessed by ESSPRI (dryness, pain, fatigue), was high, with a mean baseline score of 5.0±2.9 (Table I). Only around 42% of patients had a patient acceptable symptom state (ESSPRI<5). Over the follow-up, a mild but statistically significant increase in mean ESSPRI (5.2±2.5) was observed (Figure 3-C).

Hydroxychloroquine and corticosteroids were used in 716 (52%) and 416 (30%) patients, respectively, whereas up to 12% of patients were treated with other immunosuppressants (Table I). Methotrexate (11%, n=150) was most commonly used, followed by azathioprine (8%, n=106), rituximab (3%, n=42) and leflunomide (2%, n=33). Secretagogues (pilocarpine) were

used by 244 patients (18%). Less frequently used treatments included mycophenolate mofetil (2%, n=28), sulfasalazine (1%, n=12), intravenous immunoglobulin (n=6), ciclosporin (n=6), cyclophosphamide (n=5), amongst others (Supplementary Table).

Discussion

Herein, we provide a detailed description of a large nationwide cohort of patients with SjD. The PORTRESS registry represents a significant advance in the systematic collection and management of clinical data for SjD patients in Portugal. As an integral part of Reuma.pt, it facilitates a standardized and comprehensive approach to documenting patient information, ensuring that all relevant clinical data is captured efficiently during routine medical practice.

Additionally, the registry's capability to document and analyse systemic activity and symptom burden over time provides a more nuanced understanding of disease progression and patient outcomes. To the best of our knowledge there are internationally around 10 other clinical registries for SjD[12], the vast majority of which do not allow for inclusion of data at each appointment during follow-up.

Besides providing a structured and consistent method for data collection, the registry's web-based nature[8] ensures easy access for healthcare providers across multiple centres, fostering collaborative efforts in patient care and research.

The inclusion of multidisciplinary evaluation tools within PORTRESS, such as those for Ophthalmology and Oral Medicine, is particularly noteworthy. These features enable a comprehensive assessment and care of patients with SjD, covering various aspects of the disease from glandular function to systemic involvement. The integration of PROs further enriches the data quality, providing insights into the patient's perspective on their disease and treatment.

The demographic profile (middle-aged women) of PORTRESS was consistent with other similar cohorts[1,13,14]. Importantly, a considerable delay in diagnosis of almost 5 years was observed, despite the vast majority of patients presenting with typical symptoms of dryness, pain and fatigue, in addition to common extraglandular features. This is in line with previous reports in other countries[15,16] and highlights one of the major unmet needs in SjD[17,18].

In the PORTRESS registry, systemic involvement — as defined by ESSDAI — was observed in the majority of patients, emphasizing the multisystemic nature of SjD. In particular, many patients presented salivary gland swelling, extraglandular disease or laboratorial features of B cell hyperactivity at a given point in the course of their disease. This has been previously shown and is one of the major advances in the last decades regarding our better understanding and finer definition of the whole picture of SjD[3,5,13].

In terms of exocrine function, a significant finding was that although most patients complained of oral dryness, a reduced salivary flow according to the classification criteria definition was present in only one-fifth of the cases. This underlines the notion that these strict cut-offs, which do not take into account other simple patient characteristics such as age, may underestimate organ impairment. In this case, it is particularly relevant as reduced salivary flow is one of the key criteria to classify patients as having SjD according to current criteria, possibly excluding patients from access to clinical trials and other observational studies.

This aspect is well demonstrated in PORTRESS, which is a real life-based registry and therefore includes all patients with a clinical diagnosis of SjD, regardless of classification criteria fulfilment. While this may be a limitation (as addressed below), it is also important to note that a considerable proportion of patients (around 40%) did not fulfil these criteria, which can be explained in a great part due to the difficulty in access to specialized ocular and oral care in most centres. Importantly, however, over 92% of patients had both typical SjD signs/symptoms and positive anti-Ro/salivary gland biopsy. We would stress that these patients are followed in rheumatology centres with significant expertise and experience in managing patients with SjD, thus not undermining the confidence in the diagnosis. On the contrary, the inclusion criteria for PORTRESS are clear and simple (SjD diagnosis) and this may be a major advantage, as it provides a better and more comprehensive view of the whole SjD population, a great part of which is excluded in most published studies[19].

We reported a significant decrease in ESSDAI over time, assessing only two timepoints (baseline and last follow-up visit). This may be due to a number of reasons. First, the fact that a stabilized ESSDAI domain present for over one year is not scored in ESSDAI[20], results in its 'artificial' reduction without translating actual patient improvement. This means that the decrease in ESSDAI score observed from baseline to follow-up, may only indicate a stabilization of the patients' systemic involvement rather than a significant improvement. Nevertheless, while systemic disease activity showed at least some stabilization over time, the symptom burden, particularly in terms of dryness, pain, and fatigue, appeared to worsen. Although small in the absolute magnitude, this finding points to a significant unmet need in the management of SjD symptom burden, despite control of systemic disease features[18,21,22].

Despite its strengths, the PORTRESS registry also highlights some challenges inherent to the collection of clinical data in a real-life setting. Since the completion of data by clinicians is voluntary, a balance must be maintained between too simple, not allowing for relevant research, and too complex, setting hurdles for completion of data during regular patient

appointments. This balance is crucial to ensure that the registry remains both practical for everyday clinical use and valuable for research purposes.

Alongside this challenge, our study has some limitations, part of which are common in routine care-based registries, such as missing data or underreporting of specific aspects of the patient follow-up. For example, a treatment that a patient only adhered to for a short period of time may not be registered, or appointments may be underreported when the patient is stable.

Furthermore, as exposed above, the inclusion of patients with a clinical diagnosis of SjD means that the diagnosis was based on clinical expertise without any external validation. Despite this limitation, it is important to highlight that classification criteria should not be used for diagnosis and that all of these patients were followed in specialized rheumatology centres. In addition, as it was shown, real-world clinical practice often does not allow for the completion of classification criteria assessment, and even patients that do not meet classification criteria may have the disease, and are surely underrepresented in current research. This limits our understanding of the full spectrum of the disease and future application of innovative emerging therapies.

Looking forward, the potential for PORTRESS to link with international databases offers exciting opportunities for broader research collaborations. Such links could facilitate large-scale studies and comparative research, thereby contributing to a more comprehensive global understanding of SjD. Additionally, the registry's role in supporting clinical trials and observational studies is crucial for advancing SjD research, particularly in identifying new therapeutic targets and evaluating the long-term efficacy and safety of treatments.

Patient viewpoint

Our patients emphasize that their quality of life is profoundly affected by persistent symptoms, which disrupt daily activities and undermine both physical and mental well-being. They highlight that while current therapies may manage disease activity, they often fail to address symptom burden and irreversible damage, resulting in frustration and a sense of neglect. Limited treatment efficacy can erode trust in healthcare systems, reducing adherence to therapy, particularly when patients feel their concerns are unacknowledged. External opinions from friends or family, scepticism about treatment effectiveness, and the financial and emotional toll of ongoing care further compound these challenges. Some patients even turn to alternative treatments, often without scientific backing, which may pose additional risks.

Patients also express concern over the exclusion of individuals who fail to meet rigid classification criteria in studies, including those with atypical symptoms or rare manifestations, perpetuating a sense of neglect. Patients worry that study results may not reflect their reality, leaving them sceptical about the applicability of emerging treatments, which can further discourage participation in research and, potentially, prompt seeking of unverified alternatives. To address these issues, patients advocate for more inclusive and flexible study designs that reflect the heterogeneity of real-world cases. They call for clear communication about the reasons for exclusion, greater emphasis on personalized treatment, and the development of complementary studies for excluded populations. They also stress the importance of active patient involvement in study design to ensure that research criteria align with the diverse realities of those living with the disease.

Conclusion

In conclusion, PORTRESS is a valuable tool that bridges the gap between clinical practice and research in SjD. Its comprehensive approach to data collection supports both the immediate clinical management of patients and the long-term research objectives essential for advancing our understanding of this complex disease. As the registry continues to evolve and expand, it holds significant potential for enhancing patient care and contributing to ground-breaking research in SjD, ultimately improving outcomes for patients with this challenging condition.

Funding, grant/award info - This work has been supported by SPCare.

Tables and Figures

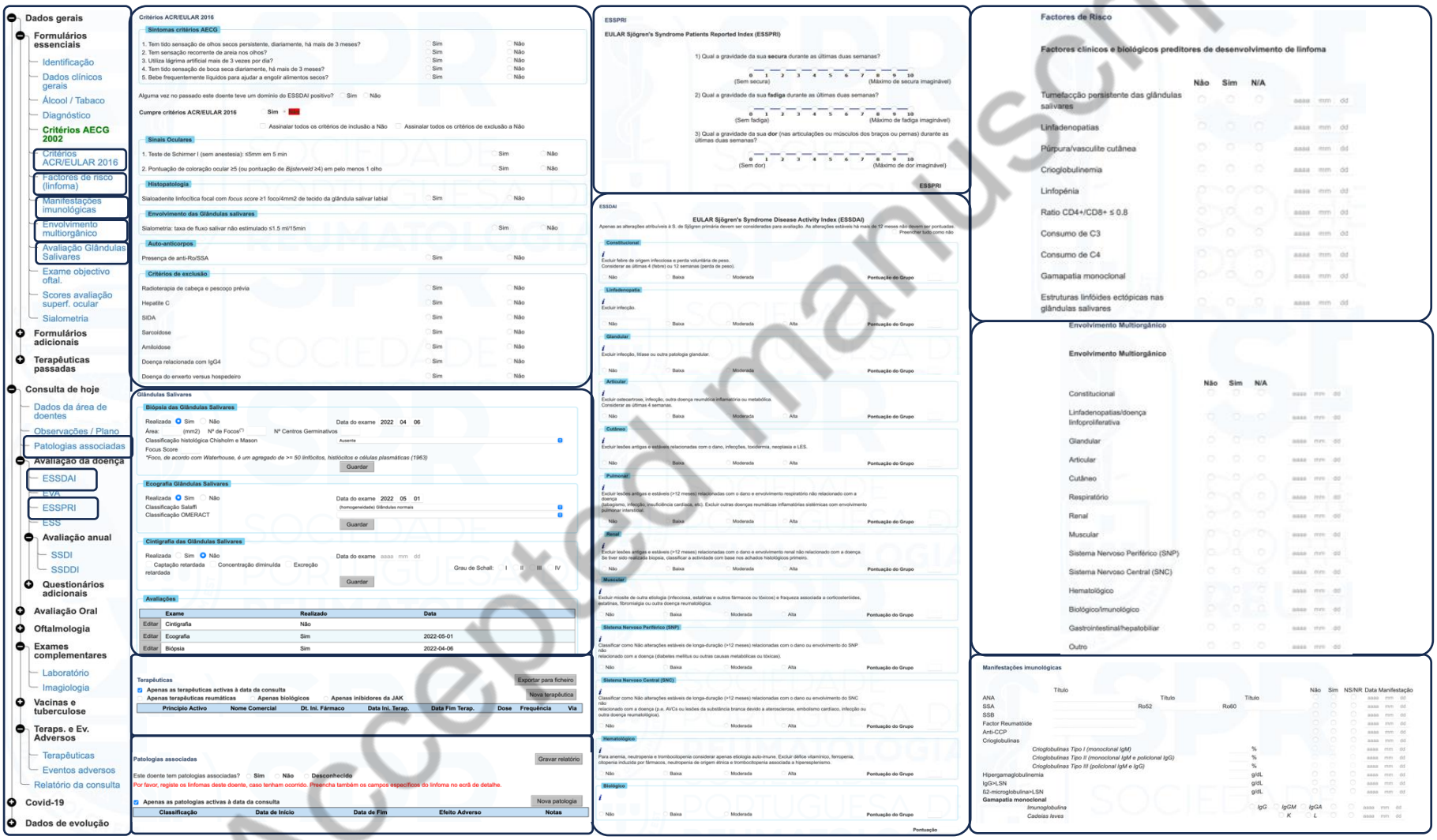
Table I – Clinical and demographic characteristics of the PORTRESS cohort

	PORTRESS cohort (n=1375)
Age at inclusion (years)	61.8±14.4
Age at diagnosis (years)	52.7±14.7
Age at symptom onset (years)	47.9±14.8
Diagnosis delay (years)	4.6±5.9
Disease duration/Follow-up (years)	13.2±8.9
Female	1300 (95)
Ethnicity, n=1115 Caucasian African ancestry Asian	 1037 (93) 63 (5) 15 (1)
Smoking habits, n=897 Never smoker Past smoker Current smoker	 699 (78) 127 (14) 71 (8)
AECG 2002 classification criteria	747/1203 (62)
ACR/EULAR 2016 classification criteria	758/1320 (57)
2002 and/or 2016 classification criteria	868/1375 (63)
ANA	1060/1166 (91)
Anti-SSA/Ro	1065/1300 (82)
Anti-Ro52	454/522 (87)
Anti-Ro60	516/563 (92)
Anti-SSB/La	541/1204 (45)
Rheumatoid factor	531/1097 (48)
Hypergammaglobulinemia	540/1105 (49)
Raised IgG	267/675 (40)
Cryoglobulinemia	64/835 (8)
ESSDAI (0-123), n=451 Baseline Follow-up	 3.0±4.4 2.1±3.7
ESSPRI (0-10), n=262 Baseline Follow-up	 5.0±2.9 5.2±2.5
PROFAD-SSI (0-56), n=437	27.4±12.9
USF <0.1ml/min	161/719 (22)
Schirmer's ≤5mm/5min	577/972 (59)
van Bijsterveld score ≥4 and/or Ocular Staining Score ≥5	86/672 (13)
Minor SG biopsy, Chisholm-Mason grade, n=568 Grade 0 Grade 1 Grade 2 Grade 3 Grade 4	 52 (9) 119 (21) 95 (17) 103 (18) 199 (35)
Minor SG biopsy, focus score, n=265	1.6±2.1
SG ultrasound EULAR-OMERACT score, n=161 Grade 0 Grade 1	 27 (17)

Grade 2	50 (31)
Grade 3	69 (43)
	15 (9)
Systemic involvement	
Constitutional	228/1234 (18)
Lymphadenopathic	138/1239 (11)
Glandular	387/1240 (31)
Articular	540/1243 (43)
Cutaneous	223/1238 (18)
Pulmonary	105/1239 (9)
Renal	34/1236 (3)
Muscular	18/1236 (2)
PNS	49/1237 (4)
CNS	20/1233 (2)
Hematologic	429/1243 (35)
Biologic*	646/1242 (52)
Gastrointestinal/Hepatobiliary	36/1234 (3)
Other**	177/1121 (16)
Treatment, n=1375	
Hydroxychloroquine	716 (52)
Corticosteroids	416 (30)
Pilocarpine	244 (18)
Methotrexate	150 (11)
Azathioprine	106 (8)
Rituximab	42 (3)
Leflunomide	33 (2)

Results presented as mean ± standard deviation or n/N (%), as appropriate; abbreviations: n – number of patients positive for the variable of interest, N – number of available values for the variable, RF – rheumatoid factor, USF – unstimulated saliva flow rate, SG – salivary gland, PNS – peripheral nervous system, CNS – central nervous system, IgG - immunoglobulin G; * characterized by laboratorial features of B cell hyperactivity; ** namely Raynaud's phenomenon, pericarditis or pulmonary hypertension among others less frequent

Figure 1 - Brief summary of the PORTRESS outline



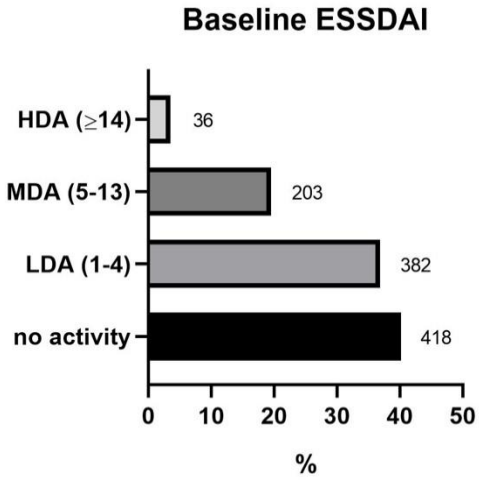


Figure 2 - Frequency of different disease activity levels at baseline. No activity (ESSDAI=0), LDA - low disease activity (ESSDAI<5), MDA - moderate disease activity (ESSDAI 5-13), HAD - high disease activity (ESSDAI≥14)

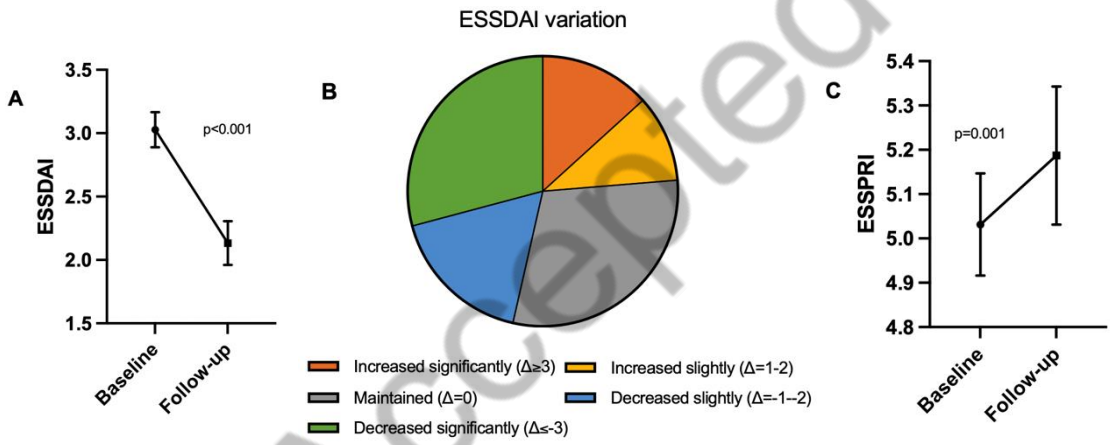


Figure 3 - Systemic disease activity assessed by ESSDAI at baseline and follow-up (A); ESSDAI variation between baseline and follow-up (B); symptom burden assessed by ESSPRI at baseline and follow-up (C)

References

1. Retamozo S, Acar-Denizli N, Rasmussen A, et al. 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. 2019;37 Suppl 1(3):97-106.

2. Bandeira M, Romão VC. Diagnosing Sjögren's disease in 2023: what is new? ARP Rheumatol. 2022;1(4):268-270.

3. Bandeira M, Silvério-António M, Khmelinskii N, Fonseca JE, Romão VC. Beyond sicca: high prevalence and predictors of baseline and worsening systemic involvement in patients with Sjögren's disease. Rheumatol Adv Pract. Published online March 6, 2024:rkae035. https://doi.org/10.1093/rap/rkae035

4. Brito-Zerón P, Flores-Chávez A, Horváth IF, et al. Mortality risk factors in primary Sjögren syndrome: a real-world, retrospective, cohort study. eClinicalMedicine. 2023;61.

5. Brito-Zerón P, Acar-Denizli N, Ng W-F, et al. How immunological profile drives clinical phenotype of primary Sjögren's syndrome at diagnosis: analysis of 10,500 patients (Sjögren Big Data Project). Clin Exp Rheumatol. 2018;36 Suppl 1(3):102-112.

6. Melchor S, Sánchez-Piedra C, Fernández Castro M, et al. Digestive involvement in primary Sjögren's syndrome: analysis from the Sjögrenser registry. Clin Exp Rheumatol. 2020;38 Suppl 1(4):110-115.

7. Juarez M, Toms TE, De Pablo P, et al. Cardiovascular risk factors in women with primary Sjögren's syndrome: United Kingdom primary Sjögren's syndrome registry results. Arthritis Care Res. 2014;66(5):757-764. doi:10.1002/acr.22227 https://doi.org/10.1002/acr.22227

8. Canhão H, Faustino A, Martins F, Fonseca JE. Reuma.pt - the rheumatic diseases portuguese register. Acta Reumatol Port. 2011;36(1):45-56.

9. Reuma.pt. Accessed March 11, 2024. https://reuma.pt/

10. Dourado E, Melo AT, Campanilho-Marques R, et al. The idiopathic inflammatory myopathies module of the Rheumatic Diseases Portuguese Register. ARP Rheumatol. 2023;2(3):188-199.

11. Ponte C, Khmelinskii N, Teixeira V, et al. Reuma.pt/vasculitis - The Portuguese vasculitis registry. Orphanet J Rare Dis. 2020;15(1). https://doi.org/10.1186/s13023-020-01381-0

12. Bandeira M, Di Cianni F, Marinello D, et al. An overlook on the current registries for rare and complex connective tissue diseases and the future scenario of TogethERN ReCONNET. Front Med. 2022;9:889997. https://doi.org/10.3389/fmed.2022.889997

13. Quartuccio L, Baldini C, Bartoloni E, et al. Correlation between ESSDAI and ClinESSDAI in a real-life cohort of patients with Sjögren's syndrome. Clin Exp Rheumatol. 2017;35(3):546-547.

14. Alegria GC, Guellec D, Mariette X, et al. Epidemiology of neurological manifestations in Sjögren's syndrome: data from the French ASSESS Cohort. RMD open. 2016;2(1). https://doi.org/10.1136/rmdopen-2015-000179

15. Meinecke A, Kreis K, Olson P, et al. Impact of time to diagnosis in patients with primary Sjögren's syndrome: a cross-sectional study. Clin Exp Rheumatol. Published online July 30, 2024. https://doi.org/10.55563/clinexprheumatol/karr2a

16. Huang YT, Lu TH, Chou PL, Weng MY. Diagnostic Delay in Patients with Primary Sjögren's Syndrome: A Population-Based Cohort Study in Taiwan. Healthcare. 2021;9(3). https://doi.org/10.3390/healthcare9030363

17. Romão VC, Talarico R, Scirè CA, et al. Sjögren's syndrome: state of the art on clinical practice guidelines. RMD open. 2018;4(Suppl 1):e000789. https://doi.org/10.1136/rmdopen-2018-000789

18. Vieira A, Grosjean A, Stone LJ, et al. Sjögren's: the European patients' community perspective. Clin Exp Rheumatol. 2021;39 Suppl 1(6):S14-S16. https://doi.org/10.55563/clinexprheumatol/8vip9k

19. Dyball S, Madenidou AV, Rodziewicz M, et al. Clinical trial eligibility of a real-world connective tissue disease cohort: Results from the LEAP cohort. Semin Arthritis Rheum. 2024;67. https://doi.org/10.1016/j.semarthrit.2024.152463

20. Seror R, Ravaud P, Bowman SJ, et al. EULAR Sjogren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjogren's syndrome. Ann Rheum Dis. 2010;69(6):1103-1109. https://doi.org/10.1136/ard.2009.110619

21. Tarn J, Lendrem D, McMeekin P, Lendrem C, Hargreaves B, Ng WF. Primary Sjögren's syndrome: Longitudinal real-world, observational data on health-related quality of life. J Intern Med. 2022;291(6):849. https://doi.org/10.1111/joim.13451

22. Dias LH, Miyamoto ST, Giovelli RA, de Magalhães CIM, Valim V. Pain and fatigue are predictors of quality of life in primary Sjögren's syndrome. Adv Rheumatol (London, England). 2021;61(1):28. https://doi.org/10.1186/s42358-021-00181-9

Supplementary material

Supplementary Table I - Frequencies of available values for the items of both classification criteria

Number of items with data available	AECG 2002 classification criteria
≤2	201 (15)
3	94 (7)
4	246 (18)
5	214 (16)
6	620 (45)
	ACR/EULAR 2016 classification criteria
≤2	495 (36)
3	172 (13)
4	173 (13)
5	535 (39)

Results presented as n (%); abbreviations: n – number of patients with information for the number of variables of interest

Supplementary Table II - Additional treatments reported in the PORTRESS cohort

	PORTRESS cohort (n=1375)
Immunosuppressive treatment	
MMF	28 (2)
Sulfasalazine	12 (1)
IVIG	6 (0)
Cyclosporine	6 (0)
Cyclophosphamide	5 (0)
Anti-TNF	5 (0)
Tacrolimus	2 (0)
Tocilizumab	1 (0)
Abatacept	1 (0)

Results presented as mean ± standard deviation or n (%), as appropriate; abbreviations: n – number of patients positive for the variable of interest, MMF – mycophenolate mofetil, IVIG – intravenous immunoglobulin, NSAIDs – non-steroidal anti-inflammatory drugs