# Primary Sjögren's syndrome in South Australia

S.A. Lyne[1,2], S. Downie-Doyle[1,3], S.E. Lester[1,3], A. Quinlivan[1], P. Toby Coates[4,5], T.P. Gordon[2,6,7], M. Rischmueller[1,3,4]

*[1]Rheumatology Department, The Queen Elizabeth Hospital, Woodville South; [2]Flinders Medical School, Flinders University, Bedford Park; [3]Rheumatology Research Group, Basil Hetzel Institute, Woodville South; [4]Adelaide Medical School, University of Adelaide; [5]Central Northern Adelaide Renal and Transplantation Service, Adelaide; [6]Immunology Department, Flinders Medical Centre, Bedford Park; [7]SA Pathology Immunology Department, Adelaide, Australia.*

*Suellen A. Lyne, MBBS*
*Sarah Downie-Doyle, BSc (Hons), PhD*
*Susan E. Lester, BSc (Hons)*
*Alannah Quinlivan, BMedSci, MBBS*
*P. Toby Coates, MBBS PhD FRACP*
*Tom P. Gordon, MBBS, PhD, FRACP*
*Maureen Rischmueller, MBBS, FRACP*

*Please address correspondence to:*
*Maureen Rischmueller,*
*Department of Rheumatology,*
*5C Tower Block,*
*The Queen Elizabeth Hospital,*
*28 Woodville Road,*
*Woodville South 5011 SA, Australia.*
*E-mail: maureen.rischmueller@sa.gov.au*

*Received on June 20, 2020; accepted in revised form on July 13, 2020.*

*Clin Exp Rheumatol 2020; 38 (Suppl. 126): S57-S63.*



**Key words:** primary Sjögren's syndrome, autoimmune diseases, South Australia, geoepidemiology, ESSDAI, congenital heart block, Ro/La autoantibodies, cryoglobulinaemia

*Funding: see page S62.*

*Competing interests: M. Rischmueller is an investigator on clinical trials in Sjögren's syndrome for BMS and Novartis. The other authors have declared no competing interests.*

## ABSTRACT

**Objective.** *To describe clinical and serological characteristics of a South Australian primary Sjögren's syndrome (pSS) cohort.*

**Methods.** *The South Australian Sjögren's Syndrome Research Clinic and Database is a clinical cohort of patients with pSS at a single site. Baseline clinical and laboratory data from 172 patients were retrospectively examined to determine their prevalence and clinical associations. Results were compared to findings from 10,500 patients from The Big Data Sjogren Project Consortium; an international, multicentre registry established in 2014, which included the South Australian data.*

**Results.** *Of 172 South Australian patients with pSS, 90.1% were female with a mean age at diagnosis of 57 years. Ocular and oral sicca symptoms were common, affecting 97.1% and 99.4% respectively. Anti-Ro ± La positivity was detected in 82.6%, ANA positivity in 77%, and in 9% of patients both ANA and ENA were negative. Mean ESSDAI was 6.8 at baseline, slightly higher than the international cohort at 6.1; the most commonly positive domains being biological, articular and glandular. Pulmonary manifestations represented the most significant morbidity over time. Lymphoma was recorded in 5.2% of patients and congenital heart block in 4 offspring of 52 patients with longitudinal follow-up (7.7%), although incomplete data likely resulted in underestimation of both.*

**Conclusion.** *Despite the relatively small sample size of the South Australian cohort, clinical and serological characteristics correspond closely with international descriptions.*

## Introduction

Primary Sjögren's syndrome (pSS) is a relatively common systemic autoimmune rheumatic disease, with a prevalence between 0.01% and 0.72% (1). pSS is characterised by lymphocytic infiltration of salivary and lacrimal glands and immune-mediated secretory dysfunction (2). Xerostomia and keratoconjunctivitis sicca are cardinal manifestations, with many patients also exhibiting systemic and extraglandular disease, with an increased risk of malignant lymphoma (3). To our knowledge, characteristics of Australian patients with pSS have never been published. Therefore, the objective of this study was to describe immunologic and clinical characteristics of the South Australian Sjögren's cohort.

## Materials and methods

The South Australian (SA) primary Sjögren's Syndrome Research Clinic and Database comprises a single site clinical cohort. Patients are referred by primary care physicians or specialists, for suspected rheumatic disease, and recruited following confirmation of a diagnosis of pSS. A repository of serum and DNA samples from all subjects enables investigation of clinical, immunological and genetic aspects of disease (4-11), the latter recently reviewed (12). Data was collected from 172 SA patients with pSS who fulfilled European consensus criteria (13) American-European Consensus Group Classification Criteria for Sjögren's syndrome (14) and 2016 ACR-EULAR Classification Criteria for pSS (15). Data collection commenced at the Flinders Medical Centre in 1991, and since 1996 has been based at The Queen Elizabeth Hospital. All participants provided informed consent for collection and usage of their data and biologic samples for research into the pathogenesis of pSS, and the study was approved by the ethics of human research committee of each contributing centre.

Data collection included demographics (gender, age, race), age at onset of sicca symptoms and diagnosis, sicca symptoms and secretory function, extra-

glandular features, salivary gland pathology, Ro/SS-A and La/SS-B autoantibodies, antinuclear antibodies (ANA), rheumatoid factor (RF), complement components C3 and C4, cryoglobulins, and disease activity using the EULAR-SS disease activity score (ESSDAI, retrospectively estimated for baseline in patients recruited prior to 2010) (16). Evaluation was conducted in accordance with the European Committee Study Group, including Schirmer's test (≤5mm in 5 minutes), Rose Bengal (>4 according to van Bijsterveld's scoring system) (17, 14), unstimulated whole salivary flow (≤1.5mL in 15 minutes), salivary scintigraphy or parotid sialography for objective evidence of salivary gland dysfunction (13). Immunological tests were conducted using standardised commercial assays. ESSDAI scores were calculated based on systemic involvement at diagnosis, and an ESSDAI domain was considered positive for any activity level ≥1 (16). Out of ESSDAI features, defined by previous studies as 26 organ-specific manifestations not currently included in the ESSDAI classification (18) were recorded at baseline. Data collected on ESSDAI activity and out of ESSDAI manifestations during follow-up visits (defined as ≥2 visits) enabled analysis of longitudinal trends.

Descriptive data are presented as frequencies and percentages for categorical variables and mean with standard deviation (SD) for continuous variables. The prevalence of a specific feature is stated as the number of cases with that feature/number of cases in which the feature was detailed. Univariate analysis using $\chi^2$ test was used to study categorical variables. T-tests were used to compare the mean age at diagnosis and mean ESSDAI. *P*-trend values were estimated in Stata v. 16.1 (StataCorp LLC, TX, USA) using the "ptrend" command. All significance tests were two-tailed and values of $p<0.05$ were considered significant.

## Results

Baseline characteristics of the SA and international cohorts are summarised in Table I. Our patients were predominantly female (90.1%) with a mean age at diagnosis of 56.8 years. Dry eyes were reported by 97.1% of patients and dry mouth in 99.4%. Objective tests for ocular dryness, including Schirmer's and Rose Bengal, were positive in 89.6% patients, and abnormal tests of salivary function in 87.1%. Of the 60 patients who underwent a minor salivary gland biopsy, 98.3% were positive and the mean focus score was 3.54.

The mean ESSDAI at baseline for the SA cohort was 6.8 *versus* 6.1 among international counterparts. As outlined in Table I, higher rates of activity were seen in the SA cohort compared to the international cohort in the biological (60.1% *vs*. 50.0%), cutaneous (15.7% *vs*. 10%), articular (53.5% *vs*. 41.0%) and glandular (48.8% *vs*. 25.0%) domains. Activity in the haematological domain was higher in the Big Data Cohort (22.0% *vs*. 14.8%), however, there was no significant difference between the remaining 7 domains. Figure 1 illustrates the percentage of patients reporting activity ≥1 in each of the 12 ESSDAI domains at baseline, according to gender, in the Australian and international cohorts. The total ESSDAI score in SA male and female patients was equal at 6.8. However, in the SA cohort, male gender was associated with higher rates of organ-specific activity in constitutional, lymphadenopathy, cutaneous, haematological, biological and PNS domains (Fig. 1).

**Table I.** Baseline characteristics of 172 patients from the South Australian Sjögren's syndrome research clinic and database and 10,500 patients from the Big Data Sjögren Project Consortium (19, 20).

| | South Australian cohort (n = 172) | | Big Data Sjögren Project (n = 10,500) | | *p* value (<0.05) |
|---|---|---|---|---|---|
| **Epidemiology** | | | | | |
| Gender (female) | 155/172 | 90.1% | 9806/10500 | 93.4% | 0.12 |
| Age at diagnosis | 56.8 ± 13.1 | | 53.1 ± 14 | | **<0.001** |
| **Glandular Involvement** | | | | | |
| Dry eye | 167/172 | 97.1% | 9684/10500 | 92.2% | **0.026** |
| Dry mouth | 171/172 | 99.4% | 9832/10500 | 93.6% | **0.003** |
| Abnormal ocular tests | 138/154 | 89.6% | 8167/9745 | 83.8% | 0.07 |
| Schirmer's test | 134/153 | 87.6% | 6668/8606 | 77.5% | **0.004** |
| Rose Bengal | 11/14 | 78.6% | 2916/3996 | 73% | 0.87 |
| Positive minor salivary gland biopsy | 59/60 | 98.3% | 6368/7777 | 81.9% | **0.002** |
| Abnormal oral diagnostic tests | 54/62 | 87.1% | 6373/8115 | 78.5% | 0.14 |
| Unstimulated whole salivary flow | 52/60 | 86.7% | 4727/6290 | 75.2% | 0.06 |
| Parotid sialography | 2/2 | 100% | 1718/2157 | 79.6% | 0.48 |
| Salivary scintigraphy | n/a | n/a | 1701/2084 | 81.6% | - |
| **Serology** | | | | | |
| (+) Ro ± La | 142/172 | 82.6% | 7917/10420 | 76% | 0.06 |
| (+) Ro | 142/172 | 82.6% | 7617/10417 | 73.1% | **0.007** |
| (+) La | 108/171 | 63.2% | 4662/10362 | 45% | **<0.001** |
| (+) ANA | 114/148 | 77.0% | 7749/9784 | 79.2% | 0.57 |
| (+) RF | 104/151 | 68.9% | 4245/8758 | 48.5% | **<0.001** |
| C3 low | 3/127 | 2.4% | 1146/8573 | 13.4% | **<0.001** |
| C4 low | 15/127 | 11.8% | 1234/8556 | 14.4% | 0.48 |
| Cryoglobulins | 6/80 | 7.5% | 342/4732 | 7.2% | 0.90 |
| **ESSDAI** (activity ≥1) | **(n = 172)** | | **(n = 10,007)** | | |
| Constitutional | 19/172 | 11.1% | 950/10007 | 9.5% | 0.58 |
| Lymphadenopathy | 15/172 | 8.7% | 863/10007 | 8.6% | 0.93 |
| Glandular | 84/172 | 48.8% | 2146/10007 | 21.4% | **<0.001** |
| Articular | 92/172 | 53.5% | 3772/10007 | 37.7% | **<0.001** |
| Cutaneous | 27/172 | 15.7% | 940/10007 | 9.4% | **0.008** |
| Pulmonary | 20/172 | 11.6% | 1043/10007 | 10.4% | 0.70 |
| Renal | 7/172 | 4.1% | 442/10007 | 4.4% | 0.97 |
| Muscular | 1/172 | 0.6% | 232/10007 | 2.3% | 0.21 |
| PNS | 9/172 | 5.2% | 600/10007 | 6.0% | 0.80 |
| CNS | 0/172 | 0% | 189/10007 | 1.9% | - |
| Haematological | 21/142 | 14.8% | 2207/9839 | 22.4% | **0.038** |
| Biological | 89/148 | 60.1% | 4931/9678 | 51.0% | **0.033** |
| **Mean ESSDAI score** | **6.8 ± 6.07** | | **6.1± 7.5** | | **0.22** |

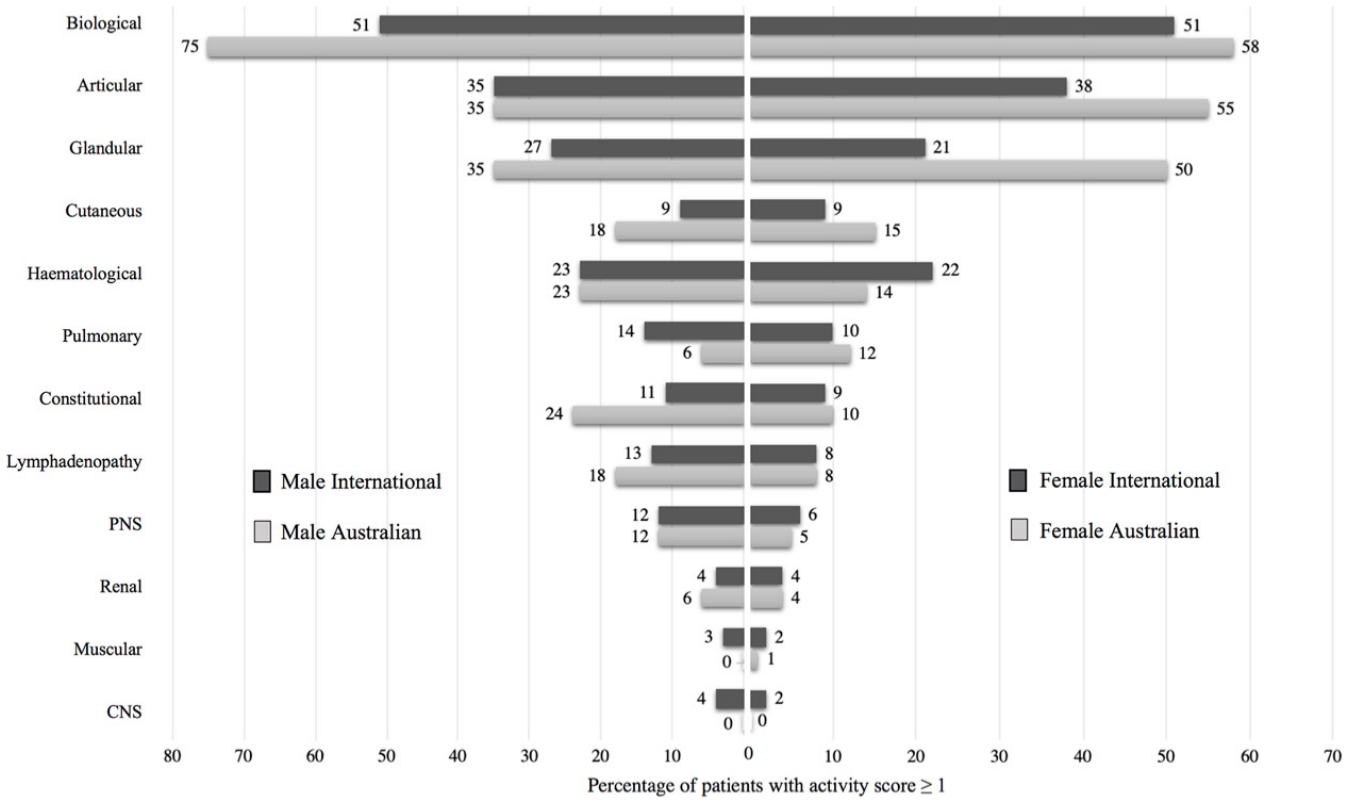


**Fig. 1.** Percentage reporting activity ≥1 in each of the 12 ESSDAI domains at baseline, according to gender, in 172 patients from the South Australian Sjögren's Syndrome Research Clinic and Database and 10,007 patients from the Big Data Sjogren Project Consortium (20).

Serologically, the presence of anti-Ro antibodies was most frequent, followed by ANA and anti-La. As demonstrated in Table II, all 172 patients were tested for anti-Ro and anti-La autoantibodies; 63.2% were Ro+La+, 19.8% were Ro+La- and 17.4% were Ro-La-. No patients tested positive for anti-La alone. There was a higher proportion of males in the seropositive group compared to Ro-La- (11.3% *vs*. 3.3%). Ro+La+ patients had a lower mean age at diagnosis (55.4 *vs*. 59.2 years), higher rates of abnormal ocular and oral tests and a higher mean ESSDAI score compared to their Ro+La- and Ro-La- counterparts. 149 patients were tested for ANA; 77.0% were positive (>1:40) and of these 91.3% were female. There were 104 RF+ patients of the 151 tested, and of these 90.4% were female. RF+ patients had a lower mean age at diagnosis (55.0 *vs*. 59.5 years) and higher rates of joint involvement (57.7% *vs*. 47.1%) than RF-negative patients. 127 patients were tested for C3 and C4, and of these 2.4% had low C3 and 11.8% had low C4. Compared to those with normal complement components, patients with low C3 or C4 had a slightly younger mean age at diagnosis (47.7 *vs*. 56.9 and 50.9 *vs*. 57.3 years, respectively). 6 of 80 patients tested (7.5%) had cryoglobulinaemia detected at baseline.

53 SA patients (30.8%) had ESSDAI data collected on more than one visit. In this cohort, mean ESSDAI at baseline was 8.1 compared to 9.0 at the most recent follow-up visit. The calculated mean ESSDAI across all visits (total 188) was 9.9±8.2. Organ-specific activity using weighted ESSDAI scores was highest in the pulmonary and articular domains, with a mean longitudinal activity score of 2.9 and 1.6 respectively. The mean longitudinal activity score among the remaining 10 domains was 0.45 by comparison.

At diagnosis and during follow-up, 52 SA patients (30.2%) reported out-of-ESSDAI manifestation and 13 (25%) reported two or more of these features. Table III lists frequencies; most common being cardiovascular including Raynaud's phenomenon, followed by digestive, neurological, ENT, pulmonary, urological and ocular.

## Discussion

Despite the relatively small sample size of the SA cohort, characteristics correspond closely to international data published through the Big Data Sjögren's Project, a multicentre registry established in 2014 (18, 19, 20, 21). Notable similarities include gender distribution with a female ratio of 90.1% *versus* 93.4% ($p$=0.12), rates of abnormal ocular tests at 89.6% *versus* 83.3% ($p$=0.07) and oral tests at 87.1% *versus* 78.5% ($p$=0.14). There was also a statistically significant difference in the rates of reported sicca, with South Australians being more likely to report dry eyes at 97.1% *versus* 92.2% and dry mouth at 99.4% *versus* 93.6% compared to their international counterparts ($p$<0.05). The reason for this observation is unclear; however, sicca is a subjectively reported experience.

The rate of Ro and La antibody positivity differed between the SA and international cohorts, at 82.6% *versus* 73.1% ($p$=0.007) and 63.2% *versus* 45% ($p$<0.001), respectively. A potential explanation is that a number of contributing investigators to the Big Data

**Table II.** Association of Ro and La autoantibodies with clinical phenotype at baseline.

| | Ro+ La+ (n=108) | Ro+ La- (n=34) | Ro- La- (n=30) | *p*-value (<0.05) |
|---|---|---|---|---|
| **Epidemiology** | n (%) | n (%) | n (%) | |
| Gender (F) | 95 (88.0) | 31 (91.2) | 29 (96.7) | 0.16 |
| Age (mean ± sd) | 55.4 ± 14.3 | 58.5 ± 12.6 | 59.9 ± 8.24 | |
| **Glandular involvement** | | | | |
| Dry eyes | 106/108 (98.1) | 31/34 (91.2) | 30/30 (100) | 0.88 |
| Dry mouth | 108/108 (100) | 33/34 (97.1) | 30/30 (100) | NA |
| Abnormal ocular tests | 87/94 (92.6) | 28/32 (87.5) | 23/28 (82.1) | 0.10 |
| Abnormal oral test | 35/36 (97.2) | 11/15 (73.3) | 8/12 (66.7) | **0.003** |
| Positive minor salivary gland biopsy | 20/20 (100) | 9/10 (90.0) | 30/30 (100) | NA |
| Focus score (mean ± sd) | 3.7 ± 0.47 | 3.4 ± 1.01 | 3.5 ± 0.73 | |
| **ESSDAI** | | | | |
| Constitutional | 13/108 (12.0) | 1/34 (2.9) | 5/30 (16.7) | 0.85 |
| Lymphadenopathy | 9/108 (8.3) | 2/34 (5.9) | 4/30 (13.3) | 0.52 |
| Glandular | 61/108 (56.5) | 11/34 (32.4) | 12/30 (40) | **< 0.001** |
| Articular | 63/108 (58.3) | 13/34 (38.2) | 16/30 (53.3) | 0.30 |
| Cutaneous | 23/108 (21.3) | 4/34 (11.8) | 0/30 (0) | **0.004** |
| Pulmonary | 15/108 (13.9) | 2/34 (5.9) | 3/30 (10) | 0.37 |
| Renal | 5/108 (4.6) | 1/34 (2.9) | 1/30 (3.3) | 0.68 |
| Muscular | 1/108 (0.9) | 0/34 (0) | 0/30 (0) | NA |
| PNS | 5/108 (4.6) | 2/34 (5.9) | 2/30 (6.7) | 0.63 |
| CNS | 0/108 (0) | 0/34 (0) | 0/30 (0) | NA |
| Haematological | 13/87 (14.9) | 6/28 (21.4) | 2/27 (7.4) | 0.52 |
| Biological | 69/92 (75.0) | 12/28 (42.9) | 8/28 (28.6) | **< 0.001** |
| ESSDAI (mean ± sd) | 7.9 ± 6.6 | 4.5 ± 4.1 | 5.3 ± 4.98 | |

**Table III.** Longitudinal out of ESSDAI manifestations recorded in the SA population (n=52).

| Percentage of patients with systemic features out of ESSDAI n=52 | n (%) |
|---|---|
| Cardiovascular features | 29 (56) |
| Raynaud's phenomenon | 23 (44.2) |
| Congenital heart block | 4 (7.7) |
| Valvular heart disease | 2 (3.8) |
| Pericarditis | 1 (1.9) |
| Digestive features | 16 (30.8) |
| Acute pancreatitis | 1 (1.9) |
| Autoimmune hepatitis | 2 (3.8) |
| Chronic gastritis | 3 (5.8) |
| Dysphagia | 10 (19.2) |
| Neurological features | 6 (11.5) |
| Autonomic dysfunction | 4 (7.7) |
| Small fibre neuropathy | 2 (3.8) |
| ENT | 5 (9.6) |
| Sinusitis | 5 (9.6) |
| Pulmonary features | 4 (7.7) |
| Pulmonary arterial hypertension | 3 (5.8) |
| Pleuritis | 1 (1.9) |
| Urological | 4 (7.7) |
| Interstitial cystitis | 4 (7.7) |
| Ocular features | 2 (3.8) |
| Orbital pseudotumor | 1 (1.9) |
| Episcleritis | 1 (1.9) |

Project, particularly dentists and oral pathologists, may have had greater access to salivary gland biopsy and thus included a higher portion of seronegative patients. Within our cohort, clinical phenotype varied depending upon ENA autoantibody combination, as outlined in Table II. Ro+La+ patients had a lower mean age at diagnosis (55.4 *vs*. 59.2 years) compared to their Ro+La- and Ro-La- counterparts and there was a higher proportion of males in the seropositive group compared to Ro-La- patients (11.3% *vs*. 3.3%). Ro-La- negative patients were more likely to report subjective sicca (100% ocular and oral); however, they had much lower rates of abnormal ocular and oral tests when compared to Ro+La+ patients (82.1% *vs*. 92.6% and 66.7% *vs*. 97.2%, respectively). There was a statistically significant difference in the rates of reported activity in the glandular, cutaneous, and biological ESSDAI domains, with highest rates recorded in Ro+La+ patients. Constitutional symptoms were more frequently reported by the Ro-La- negative group; however, this observation did not meet statistical significance.

Observed differences in disease expression between the two cohorts could in part result from ascertainment bias, as recruitment through a tertiary referral centre could result in patients with more systemic disease. In addition, higher age at diagnosis in the SA cohort may have led to the observation of more advanced disease at baseline. There is a historical bias towards more Ro/La positivity in the SA pSS cohort, which is reflected in Table I. Given the well-known role of ultraviolet radiation (UVR) in triggering anti-Ro/La-related cutaneous disease in pSS and SLE, notably subacute cutaneous lupus erythematosus (SCLE), we speculate that geographical factors such as climate and UVR exposure may account in part for the more prevalent cutaneous involvement in the SA cohort compared with the colder European climate.

Rates of ANA positivity were similar in the SA and International cohorts (77.0% *vs*. 79.2%). Data from SA demonstrated that ANA is not a useful screening test in pSS: ANA was negative in 34/149 (23%) of our patients, suggesting that 1 in 5 would be missed if ANA was relied upon as a screening tool. Furthermore, a positive ANA did not predict a positive ENA, as 53% of ANA-negative patients tested positive for anti-Ro. Disease activity was still moderate in ANA-negative patients, with an ESSDAI score of 5.1 compared to 7.0 in their ANA+ counterparts. There was a trend towards higher focus score in ANA-negative patients at 3.7 *vs*. 3.4, although this did not reach statistical significance. 16 patients (9%) of our SA cohort were both ANA and ENA negative, requiring positive salivary gland biopsy for diagnosis.

Certain serological markers, including RF, low C3/C4 and the presence of cryoglobulins, are known to be associated with higher ESSDAI and risk of progression to lymphoma (22). The SA data does not reflect all of these findings; although the small sample size limits meaningful analysis. Mean ESSDAI scores were comparable in patients with low C3 and low C4 and did not differ significantly from that of the over-all SA cohort (6.5 *vs*. 6.5 *vs*. 6.8). However, a significantly higher mean ESSDAI was observed in those with positive cryoglobulins (11.2). Cryoglobulinaemic vasculitis manifested in various forms, including palpable purpura, peripheral neuropathy, mononeuritis multiplex, gallbladder and gastro-

intestinal tract (haematochezia), and glomerulonephritis (Fig. 2).

In our cohort, 9 patients (5.2%) are known to have developed lymphoma; however, due to the small case number, no discernible pattern in baseline clinical or serological profiles was identified. Notably, only one had lymphadenopathy documented at baseline. Lymphoma cases comprised 1 mucosa-associated lymphoid tissue (MALT) lymphoma localised to the right parotid gland; 4 diagnoses of low-grade B-cell Non-Hodgkin Lymphoma (NHL) presenting in inguinal lymph nodes, mediastinal lymph nodes, thigh lymphocytoma and bone marrow biopsy; one stage 3A follicular lymphoma presenting in inguinal nodes, and two cases of diffuse large B-cell Lymphoma (DLBCL). One case of DLBCL was stage 4 at diagnosis, initially detected as a parotid mass and cavitating lung lesion, and the other was stage 1A, presenting with an inguinal mass. The final case was not further specified. The frequency of lymphoma in the SA cohort is likely to be underestimated, as not all patients were followed up and lymphoma data has not been ascertained.

Higher baseline ESSDAI scores are linked with adverse clinical outcomes, making the ESSDAI score an important prognostic tool (23). ESSDAI features reported in the SA data closely mirror international figures with a mean baseline ESSDAI of 6.8 in SA compared to 6.1 internationally ($p$=0.22). Biological, articular and glandular domains are universally the most frequently reported (ESSDAI activity ≥1). There was however, a statistically significant increase in the reporting of each of these domains in SA compared to the global data, with biological 60.1% *versus* 50.0%, articular 53.5% *versus* 41.0% and glandular 48.8% *versus* 25.0%. Activity ≥1 in the pulmonary domain was only reported in 11.6% of SA patients at baseline, however, it is evident that over time pulmonary complications have the most significant morbidity, with the highest longitudinal organ-specific activity score. Pulmonary manifestations reported in our cohort include cystic lung disease with lymphocytic interstitial pneumonitis (n=6),

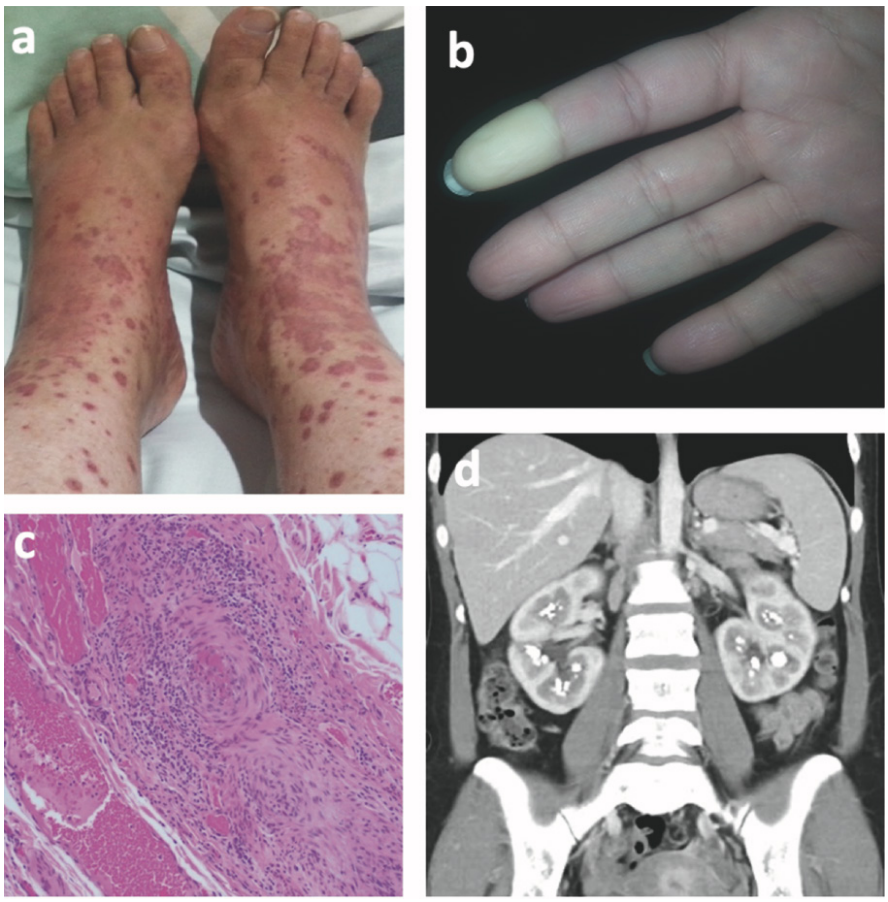


**Fig. 2.** 39-year old female with primary Sjögren's syndrome-related cryoglobulinaemic vasculitis. **a**: Cutaneous palpable purpura; **b**: Raynaud's phenomenon; **c**: Vasculitis of the gall bladder wall; **d**: Nephrocalcinosis secondary to distal renal tubular acidosis and tubulointerstitial nephritis.

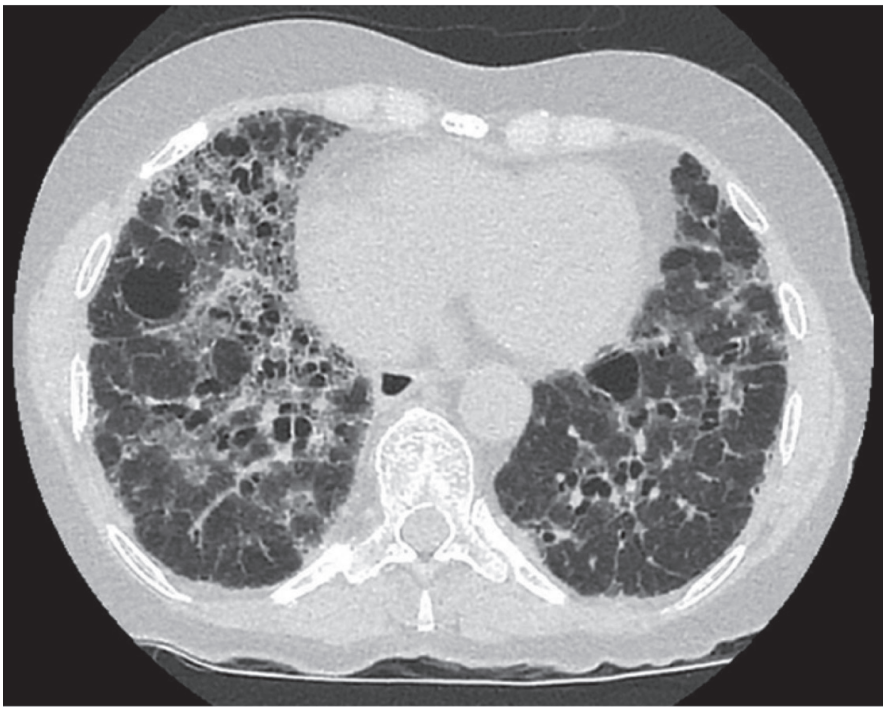

**Fig. 3.** Lymphocytic interstitial pneumonia and pulmonary fibrosis in a 68-year old woman with primary Sjögren's syndrome.

some with progression to fibrosis (Fig. 3), interstitial lung disease with NSIP pattern (n=3), bronchiolitis obliterans with bronchiectasis (n=3) and one patient with systemic lupus erythematosus (SLE) overlap had shrinking lung syndrome. Treatments have included corticosteroids, disease modifying antirheumatic drugs including mycophenolate mofetil, cyclophosphamide, and rituximab.

Studies suggest that out of ESSDAI manifestations are associated with more severe systemic disease (18). Recognition of these manifestations is therefore crucial to stratify risk and monitor for complications (2). In SA there was a trend to more severe disease activity in patients with out of ESSDAI features, with mean ESSDAI of 7.6 *vs*. 6.4; however, this difference did not meet statistical significance. Cumulative frequency of out of ESSDAI manifestations has been recorded at follow-up visits, enabling analysis of longitudinal trends in 52 of our patients. Consistent with international data, Raynaud's phenomenon is the most frequently reported, affecting 44% in our cohort (18). 3 patients in our cohort had neonates with confirmed cases of congenital heart block (CHB), and 2 children from one mother were affected (n=4). One of these infants subsequently died at 10 weeks of age. 2 additional cases of suspected CHB were recorded, each resulting in neonatal death. In total, 11 unexplained antenatal and neonatal deaths were recorded amongst 5 patients (7 miscarriages, 2 stillbirths and 2 neonatal deaths). 1 patient had a baby with suspected neonatal lupus erythematosus, presenting as a skin rash in the post-partum period.

There are several limitations to this study. Firstly, the small sample size of the SA cohort results in limited meaningful statistical analysis. Missing data further limits interpretation. The prolonged time period of data collection also creates inconsistencies, due to the evolution of classification criteria and laboratory testing over this time. Retrospective analysis has limitations, particularly with regards to estimation of ESSDAI scores, as this was only introduced in 2010. Furthermore, absence of longitudinal data on 70% of patients leads to underestimation of the frequency of sequelae such as neonatal lupus erythematosus and lymphoma.

## Conclusions

This is the first report describing characteristics of an Australian cohort of patients with pSS. Despite the relatively small sample size, disease characteristics correspond closely to international counterparts. Our results suggest that ANA is not a useful screening tool for pSS. A significant number of patients will have negative serology for Ro and La antibodies and require objective measures of ocular and oral dryness, and salivary gland biopsy, to confirm the diagnosis- currently underutilised in Australian rheumatology teaching and practice. Out of ESSDAI manifestations were present in more than 25% of our cohort, with a trend towards more severe systemic disease, and should therefore be evaluated when assessing patients with pSS.

Longitudinal clinical cohorts incorporating clinicopathological data are of increasing importance in chronic diseases, particularly pSS which is characterised by varying clinical phenotype, significant morbidity and no specific treatments. Learnings from these cohorts will continue to inform research into aetiopathogenesis and biomarkers for risk stratification and as tools for the development of novel therapeutics (24, 25). The SA Sjögren's cohort has recently been used to recruit subjects for combined proteomic and transcriptomic analyses of rheumatoid factors and type 2 mixed cryoglobulins with identification of peptide biomarkers for tracking pathogenic RF clones (26); furthermore lymphoma driver mutations were identified in RF+ specific B-cell clones providing a novel explanation for their evolution as pathogenic species in Sjögren's syndrome (27).

Geographical differences between pSS cohorts provide insights into disease causation and expression, and are critical to enabling best practice management (20, 28). Expansion of the SA Primary Sjögren's Syndrome cohort, and establishment of a national Australian Sjögren's Registry and Repository, is a critical next step, which will provide a platform for further basic scientific discovery, translational research, and recruitment of patients for investigator-led and industry sponsored clinical trials.

## Acknowledgements

We wish to thank our patients, who have been generous with their time and enthusiastic in supporting our research programme.

## Funding

Support for equipment was received from the Rebecca L. Cooper Medical Research Foundation and The Queen Elizabeth Hospital Research Foundation, and for various projects from Flinders Medical Centre Research Foundation, Arthritis Australia, Flinders University, and the National Health and Medical Research Council.

## References

1. BRITO-ZERÓN P, BALDINI C, BOOTSMA H *et al*.: Sjögren syndrome. *Nat Rev Dis Primers* 2016; 2:16047.
2. RISCHMUELLER M, TIEU J, LESTER S: Primary Sjögren's syndrome. *Best Pract Res Clin Rheumatol* 2016: 30: 189-220.
3. ABROL E, GONZÁLEZ-PULIDO C, PRAENA-FERNÁNDEZ JM *et al*.: A retrospective study of long-term outcomes in 152 patients with primary Sjögren's syndrome: 25-year experience. *Clin Med* 2014; 14: 157-64.
4. RISCHMUELLER M, LESTER S, CHEN Z *et al*.: HLA class II phenotype controls diversification of the autoantibody response in primary Sjögren's syndrome. *Clin Exp Immunol* 1998; 111: 365-71.
5. COATES T, SLAVOTINEK JP, RISCHMUELLER M *et al*.: Cerebral white matter lesions in primary Sjögren's syndrome: a controlled study. *J Rheumatol* 1999; 26: 1301-5.
6. WATERMAN SA, GORDON TP, RISCHMUELLER M: Inhibitory effects of muscarinic receptor autoantibodies on parasympathetic neurotransmission in Sjögren's syndrome. *Arthritis Rheum* 2000; 43: 1647-54.
7. CAI FZJ, LESTER S, LU T *et al*.: Mild autonomic dysfunction in primary Sjögren's syndrome: a controlled study. *Arthritis Res Ther* 2008; 10: R31.
8. LESTER S, MCLURE C, WILLIAMSON J, BARDY P, RISCHMUELLER M, DAWKINS RL: Epistasis between the MHC and the RCA-alpha block in primary Sjögren's syndrome. *Ann Rheum Dis* 2008; 67: 849-54.
9. USMANI ZA, HLAVAC M, RISCHMUELLER M *et al*.: Sleep disordered breathing in patients with primary Sjögren's syndrome: A group-controlled study. *Sleep Med* 2012; 13: 1066-70.
10. LESTER S, STOKES L, SKARRATT K *et al*.: Epistasis with HLA DR3 implicates the

P2X7 receptor in the pathogenesis of primary Sjögren's syndrome (pSS). *Arthritis Res Ther* 2013; 15: R71.
11. LESSARD CJ, LI H, ADRIANTO I *et al*.: Variants at multiple loci implicated in both the immate and adaptive immune responses are associated with Sjögren's syndrome. *Nat Genet* 2013; 45: 1284-92.
12. HARRIS VM, SCOFIELD RH, SIVILS KL: Genetics in Sjögren's syndrome: where we are and where we go. *Clin Exp Rheumatol* 2019; 37 (Suppl. 118): S234-9.
13. VITALI C, BOMBARDIERI S, MOUTSOPOULOS HM *et al*.: Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. *Arthritis Rheum* 1993; 36: 340-7.
14. VITALI C, BOMBARDIERI S, JONSSON R *et al*.: Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002; 61: 554-8.
15. SHIBOSKI CH, SHIBOSKI SC, SEROR R *et al*.: 2016 American College of Rheumatology/ European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. *Arthritis Rheumatol* 2017; 69: 35-45.
16. SEROR R, RAVAUD P, BOWMAN SJ *et al*.: EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. *Ann Rheum Dis* 2010; 69: 1103-9.
17. VAN BIJSTERVELD OP: Diagnostic Tests in the Sicca Syndrome. *Arch Ophthalmol* 1969; 82: 10-4.
18. 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. 118): S97-106.
19. BRITO-ZERÓN P, ACAR-DENIZLI N, NG WF *et al*.: How immunological profile drives clinical phenotype of primary Sjögren's syndrome at diagnosis: analysis of 10,500 patients (Sjögren Big Data Project). *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S102-12.
20. BRITO-ZERÓN P, ACAR-DENIZLI N, NG WF *et al*.: Epidemiological profile and north-south gradient driving baseline systemic involvement of primary Sjögren's syndrome. *Rheumatology* (Oxford) 2019 Dec. 24.
21. ACAR-DENIZLI N, KOSTOV B, RAMOS-CASALS M: The Big Data Sjögren Consortium: a project for a new data science era. *Clin Exp Rheumatol* 2019; 37 (Suppl. 118): S19-23.
22. VIVINO FB: Sjögren's syndrome: Clinical aspects. *Clin Immunol* 2017; 182: 48-54.
23. RAMOS-CASALS M, BRITO-ZERÓN P, SOLANS P *et al*.: Systemic involvement in primary Sjögren's syndrome evaluated by the EULAR-SS disease activity index: analysis of 921 Spanish patients (GEAS-SS Registry). *Rheumatology* (Oxford) 2014; 53: 321-31.
24. GOULES AV, EXARCHOS TP, PEZOULAS VC *et al*.: Sjögren's syndrome towards precision medicine: the challenge of harmonisation and integration of cohorts. *Clin Exp Rheumatol* 2019; 37 (Suppl. 118): S175-84.
25. CAFARO G, CROIA C, ARGYROPOULOU OD *et al*.: One year in review 2019: Sjögren's syndrome. *Clin Exp Rheumatol* 2019; 37 (Suppl. 118): S3-15.
26. WANG J, REED J, COLELLA A *et al*.: Molecular Profiling and Clonal Tracking of Secreted Rheumatoid Factors in Primary Sjögren's Syndrome. *Arthritis Rheum* 2018; 10: 1617-25.
27. SINGH M, JACKSON K, WANG J *et al*.: Lymphoma driver mutations in the pathogenic evolution of an iconic human autoantibody. *Cell* 2020; 180: 1-17.
28. BRITO-ZERÓN P, ACAR-DENIZLI N, ZEHER M *et al*.: Influence of geolocation and ethnicity on the phenotypic expression of primary Sjögren's syndrome at diagnosis in 8310 patients: a cross-sectional study from the Big Data Sjögren Project Consortium. *Ann Rheum Dis* 2017; 76: 1042-50.