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ORIGINAL RESEARCH

Clinical Implications of Antinuclear Antibody (ANA) and Anti-Ro/Anti-La Antibody Profile in Patients with Primary Sjögren's Syndrome: A Multicenter Cross-Sectional Study of a National Egyptian Cohort

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Background: Primary Sjögren's Syndrome (pSS) is a systemic autoimmune disease that predominantly impacts the exocrine glands. It is characterized by a diverse clinical manifestation and the existence of various autoantibodies. There is a lack of studies assessing the primary pSS phenome driven by anti-Sjögren syndrome autoantibodies in Africa, particularly in Egypt.

Objective: This study aims to evaluate the clinical implications of antinuclear antibodies (ANA) and anti-Ro/anti-La autoantibodies in an Egyptian national cohort of pSS patients.

Methods: We conducted a cross-sectional analysis of pSS patients, comparing clinical manifestations and disease severity based on serological profiles.

Results: A total of 301 pSS patients (mean age: 45.6±10.2 years; F:M ratio 7.4:1) were included. Patients with positive ANA (59.5%) had a higher prevalence of anti-Ro (p=0.001) and anti-La (p=0.0001) antibodies, along with lower rates of dry eyes (p=0.04) and enlarged parotid glands (p=0.001). Corticosteroid and azathioprine use was more frequent in ANA-positive patients (p=0.017, p=0.003). Double-positive anti-Ro/anti-La patients exhibited higher rates of dry mouth (p=0.045), articular manifestations (p<0.0001), fibromyalgia (p=0.001), RF positivity (p<0.001), and C4 consumption (p<0.001).

Conclusion: Patients with pSS exhibit distinct clinical and laboratory profiles based on their autoantibody status, emphasizing the importance of immunological assessment for disease management.

Keywords: primary Sjögren's syndrome, antinuclear antibody, anti-Ro, anti-La, Egypt

Introduction

Sjögren's disease (SS) is a systemic chronic autoimmune exocrinopathy, leading to dry mouth and dry eyes, but also encompassing a broad spectrum of extraglandular manifestations.[1] SS is the most prevailing autoimmune disease after rheumatoid arthritis (RA)[2] with a prevalence of 1:200.[3] SS can occur alone in primary SS (pSS) or in conjunction with other connective tissue diseases (CTDs), such as RA, systemic lupus erythematosus (SLE) and systemic sclerosis (SSc).[4] Primary SS causes dry mouth "xerostomia" and eyes "xerophthalmia", and mainly affects females between the ages of 40 and

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60 years.[5] It is characterized by the T-cell-mediated hyperactivation of B-cells and cytokine production. It can progress from an asymptomatic, indolent course, with glandular involvement, to systemic manifestations beyond the glands such as pulmonary and articular involvement, up to lymphoma development.[6] Such systemic manifestations have diagnostic and prognostic significance necessitating prompt identification and management to ensure effective care.[7] However, it is a condition that should not be overlooked, as patients may develop serious extra-glandular complications, such as lymphomas.[8]

Antinuclear antibody (ANA) is prevalent in pSS and has been linked to extraglandular manifestations, hypergammaglobulinemia, and a high frequency of antibodies against extractable nuclear antigens (ENAs).[9] The most prevalent anti-ENA antibodies in pSS patients are directed against Ro/SSA and La/SSB.[10] The existence of these antibodies is an essential component of the 2002 American-European Consensus Group (AECG) classification criteria,[11] the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria,[12] and the 1999 revised Japanese Ministry of Health criteria for pSS.[13] In established disease, anti-Ro/SSA and anti-La/SSB antibodies may be identified in 33–74% and 23–52% of patients, respectively, and are associated with a more aggressive clinical and immunologic phenotype, indicating a more severe progression or poorer prognosis.[14] Furthermore, circulating anti-Ro/SSA and anti-La/SSB antibodies have been linked to a worse cardiovascular risk profile in populations of pSS patients.[15]

The presence of these antibodies, alone or collectively, may indicate certain specific characteristics of pSS and responsiveness to treatment. Consequently, the autoantibody profile may indicate distinct phenotypes of pSS. However, their precise role in pSS pathogenesis and their impact on disease phenotypic expression remain areas of ongoing investigation. Thus, a deeper understanding of the role of these antibodies in pSS may facilitate earlier diagnosis, enabling clustering of patients and opening new therapeutic avenues to address the unmet needs of the disease.[6,16] The extent to which they shape the clinical spectrum of pSS, particularly in different ethnic populations, requires further elucidation. The majority of studies on pSS autoantibodies have been conducted in non-African populations, leaving a relative paucity of data on the implications of these autoantibodies in African and Middle Eastern cohorts, including Egyptian patients.

In our clinical experience of managing pSS patients in Egypt, we have observed variations in disease presentation between individuals who test positive for anti-Ro and/or anti-La autoantibodies and those who do not. Some of these variations appear to diverge from the patterns classically described in non-African populations, suggesting possible ethnic or geographic influences on pSS phenotypic expression. Given the evolving landscape of Sjögren's syndrome research, with increasing insights into both classical and novel correlates of anti-Ro and anti-La autoantibodies, it is imperative to examine these associations in an Egyptian pSS cohort. This study aims to assess the influence of ANA, anti-La, and anti-Ro autoantibodies on the clinical phenotype and disease manifestations in Egyptian patients with pSS. By doing so, we seek to bridge existing knowledge gaps and provide insights into potential population-specific differences in disease expression.

Materials and Methods

Study Design, Setting and Population

This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. This multicenter cross-sectional study was conducted by the Egyptian College of Rheumatology (ECR) pSS study group, which coordinates national efforts to standardize the diagnosis and management of pSS across Egypt. A total of 16 rheumatology centers, all affiliated with the ECR, participated in the recruitment of adult pSS patients between 2023 and 2024. These centers represent diverse geographic regions across Egypt, covering multiple governorates, reflecting the ECR's role in unifying clinical practices and facilitating large-scale collaborative research. *All clinical data were systematically collected and stored in a centralized electronic database established by the ECR pSS study group specifically for this national cohort study.* All patients diagnosed with pSS after the age of 16 years by fulfilling were included.

To ensure diagnostic specificity, patients with conditions that may mimic pSS were excluded. This included those with: (1) ocular disorders (glaucoma on topical medications, ocular cicatricial pemphigoid, chronic anterior uveitis, or prior ocular surgery); (2) systemic conditions associated with sicca symptoms (eg, chronic hepatitis C infection,

sarcoidosis, or IgG4-related disease); and (3) other autoimmune diseases (eg, rheumatoid arthritis, systemic lupus erythematosus, or systemic sclerosis).

Ethical Consideration

The study was approved by the local ethical committee of Aswan University (Asw.Uni. / 1008/ 11/ 24) in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all study participants prior to their inclusion in the research.

Data Collection

Trained rheumatologists used standardized spreadsheet to ensure consistent data collection. To ensure data quality, all investigators completed protocol-specific training before study initiation. The electronic system incorporated mandatory fields and validation checks to minimize missing or inconsistent data. We implemented several measures to reduce bias: strict exclusion criteria eliminated patients with overlapping autoimmune conditions, standardized laboratory methods were documented across all centers, and objective diagnostic tests (Schirmer's test and histopathology) were performed where clinically indicated to confirm pSS diagnosis.

Demographic Characteristics, Clinical and Laboratory Data

Study participants' sociodemographic characteristics, including their gender, age and geolocation were collected. Variables essential for characterizing the disease phenotype including ocular and oral dryness, clinical disease features, ocular and oral tests, ANA were captured. Immunological features such as rheumatoid factor (RF), anti-Ro and anti-La antibodies, complements (C3 and C4) levels were measured according to the local standard laboratories. Diagnostic ocular and oral tests as well as salivary gland biopsy were conducted according to the recommendations (if performed).

Therapeutic Data

The current therapeutic data, including glucocorticoids, immunosuppressants (such as methotrexate, antimalarials, cyclophosphamide, sulfasalazine, azathioprine, leflunomide), and biologics were reported.

Statistical Analysis

The databases from each center were harmonized and pre-processing techniques such as detecting and treating outliers, influential observations, errors, and dealing with missing data were applied. Data on a standardized data sheet stored in an electronic database were analyzed. Statistical Package for Social Sciences (SPSS) version 25 was used for analysis. Data were expressed as frequencies and percentages or as mean and standard deviation. Comparisons were performed using the Chi-square test, Mann–Whitney *U*-test, or analysis of variance (ANOVA). A p-value of less than 0.05 was considered statistically significant.

Results

General Characteristics of the Study Population

A total of 301 patients with pSS were included in the study, mean age of 45.6±10.2 years and 265 were females and 36 were males (F:M 7.4:1). Figure 1 presents the participant selection flowchart, illustrating the screening process, exclusion criteria, and final cohort stratification by autoantibody status. The mean age at disease diagnosis was 41.4±9.3 years. Mean disease duration was 4.6 years. 59.5% pSS patients had ANA positive, while 41.9% had double positive anti-Ro and anti-La.

Geolocation of the cases from 16 rheumatology centres revealed the distribution across Egypt. There was a significant difference in age at disease diagnosis across the included centers ($p<0.0001$), where pSS patients in Aswan had the oldest age at disease diagnosis (46.2±9.6 years), while the younger patients at disease diagnosis were identified in Giza (28.4±9.1 years). Highest autoantibodies, double anti-Ro and anti-La, ANA and RF positivity were in Minia (87.8%, 82.9% and 90.2% respectively; $p<0.0001$).

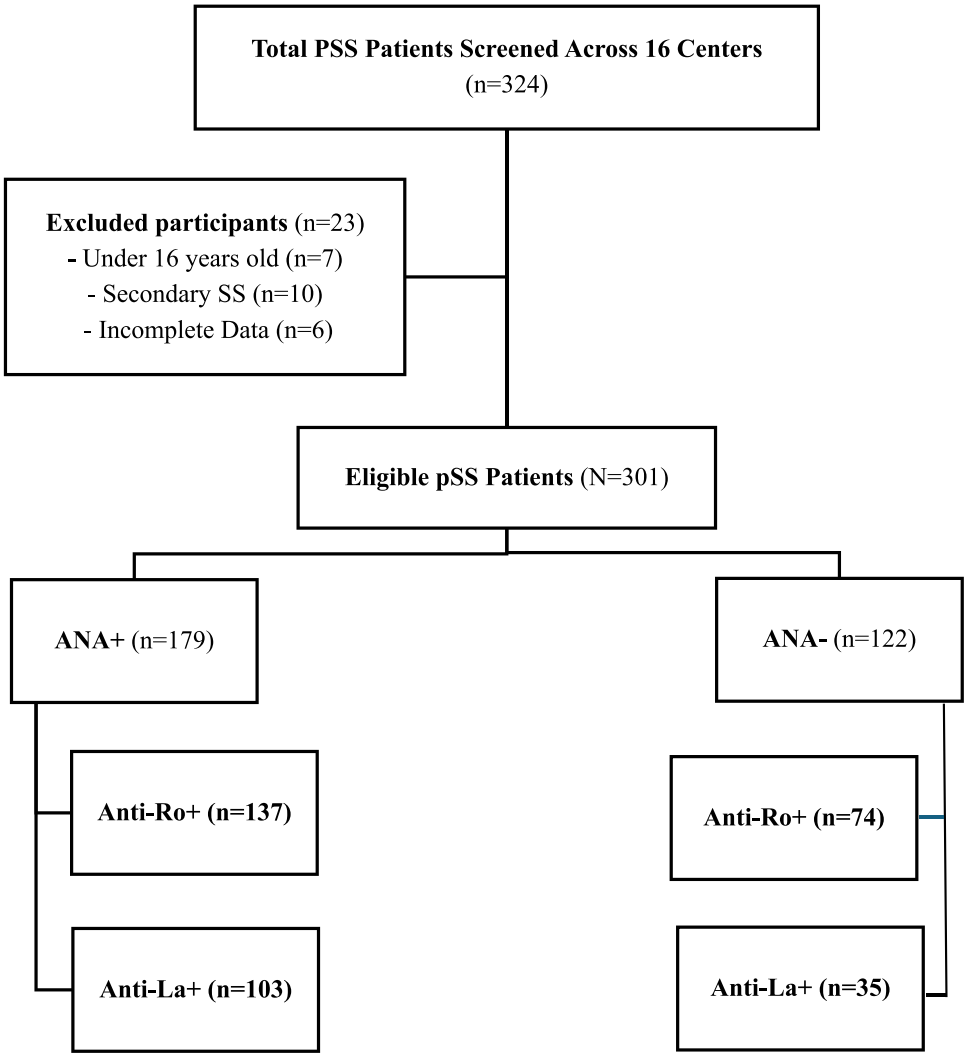

Figure 1 The flowchart of the study. Flowchart illustrating the study design, patient inclusion process, and final stratification by autoantibodies positivity.
Abbreviations: pSS, Primary Sjögren's Syndrome; ANA, Antinuclear antibodies.

Phenotypic Analysis Based on Autoantibody Profiles

Based on their ANA positivity, Table 1 illustrates the characteristics of pSS patients. No statistically significant difference was observed between patients with positive and negative ANA in terms of gender ($p = 0.40$) or age at disease diagnosis ($p = 0.14$). The prevalence of fibromyalgia syndrome ($p = 0.001$) positivity for anti-Ro ($p = 0.001$), anti-La ($p =<0.0001$), double anti-Ro and La ($p <0.0001$), and RF ($p <0.0001$) was significantly higher in ANA positive patients. The administration of corticosteroids and azathioprine was also significantly higher in patients with positive ANA ($p = 0.017$ and 0.003, respectively). Conversely, patients who had positive ANA had a statistically significant lower prevalence of dry eyes and enlarged parotid glands (p=0.04, 0.001, respectively).

The difference between pSS patients with double positive and single positive anti-Ro and anti-La antibodies is clearly shown in Table 2. There were no statistically significant differences between the two groups regarding gender and age at disease diagnosis. The presence of spontaneous abortions (p= 0.045), dry mouth (p= 0.045) and articular manifestations ($p<0.0001$) was statistically significantly higher in double positive group. In terms of lab results, patients who had double-positive anti-Ro and anti-La had higher levels of platelets ($p = 0.006$), ANA positivity ($p < 0.001$), positive RF status ($p < 0.001$), and C4 consumption ($p < 0.001$). Additionally, corticosteroids ($p<0.001$), methotrexate (p=0.003), and azathioprine ($p<0.001$) administration were statistically significantly higher among patients with double positive anti-Ro

Table 1 Characteristics of the Primary Sjögren's Syndrome Patients with and Without Anti-Nuclear Antibody Positivity (n=301)

Variable	pSS Patients (n=301)	pSS with Positive ANA (n=179)	pSS with Negative ANA (n=122)	*P value*
Sociodemographic data				
Age (years)	45.6±10.2	46.6±9.3	44.3±11.1	0.07
Gender F:M	265:36 (7.4:1)	160:19 (8.4:1)	105:17 (6.2)	0.40
Clinical data				
Disease duration (years)	4.6±4.03	5.3±4.3	3.8±3.5	**0.004**
Age at disease diagnosis (years)	41.4±9.3	42.1±8.2	40.4±10.6	0.14
Spontaneous abortions (n=265)	28 (10.6)	21 (11.7)	7 (5.7)	0.06
Hypertension	31 (10.3)	17 (9.5)	14 (11.5)	0.59
Diabetes	19 (6.3)	6 (3.4)	13 (10.7)	**0.02**
Clinical manifestations				
Dry eyes	283 (94)	167 (93.3)	116 (95.1)	**0.04**
Dry mouth	268 (89)	163 (91.1)	105 (86.1)	0.34
Enlarged parotid gland	133 (44.2)	64 (35.8)	69 (56.6)	**0.001**
Lymphadenopathy	75 (24.9)	44 (24.6)	31 (25.4)	0.70
Mucocutaneous manifestations	103 (34.2)	69 (38.5)	34 (27.9)	0.12
Articular manifestations	121 (40.2)	78 (43.6)	43 (35.2)	0.25
Pulmonary manifestations	58 (19.3)	39 (21.8)	19 (15.6)	0.24
Cardiac manifestations	23 (7.6)	13 (7.3)	10 (8.2)	0.97
Gastrointestinal manifestations	54 (17.9)	36 (20.1)	18 (14.8)	0.09
Renal manifestations	21 (7)	13 (7.3)	8 (6.6)	0.90
Neurological manifestations	73 (24.3)	50 (27.9)	23 (18.9)	0.08
Fibromyalgia syndrome	16 (5.3)	12 (6.7)	4 (3.3)	0.14
Laboratory data				
Hemoglobin (g/dl)	11.04±1.4	11.1±1.3	10.9±1.5	0.19
TLC ($x10^3/mm^3$)	6.03±2.2	5.8±2.2	6.3±2.2	0.14
Platelets ($x10^3/mm^3$)	246.2±87.3	259±85.6	229.9±87.1	**0.016**
ESR ($mm/1^{st}$ hr)	45.2±24.9	43.8±23.9	47.1±26.1	0.35
Creatinine (mg/dl)	1.06±0.91	1.19±1.17	0.88±0.24	**0.007**
AST (U/L)	25.8±14.3	25.9±12.6	25.5±16.3	0.86
ALT (U/L)	30.3±21.3	30.4±19.3	30.06±23.9	0.92
SUA	5.3±1.5	5.75±1.48	5.14±1.52	0.16
Anti-Ro	211 (70.1)	137 (76.5)	74 (60.7)	**0.001**

(*Continued*)

Table 1 (Continued).

Variable	pSS Patients (n=301)	pSS with Positive ANA (n=179)	pSS with Negative ANA (n=122)	*P value*
Anti-La	138 (59.8)	103 (57.5)	35 (28.7)	**<0.0001**
Anti-Ro and anti-La	126 (41.9)	95 (53.1)	31 (25.4)	**<0.0001**
RF	145 (48.2)	106 (59.2)	39 (32)	**<0.0001**
Low C3	18 (6)	16 (8.9)	2 (1.6)	**0.003**
Low C4	68 (22.6)	54 (30.2)	14 (11.5)	**<0.0001**
Therapeutic data				
Corticosteroids	82 (27.2)	58 (32.4)	24 (19.7)	**0.017**
Methotrexate	80 (26.6)	51 (28.5)	29 (23.8)	0.15
Antimalarials	163 (54.2)	96 (53.6)	67 (54.9)	0.46
Cyclophosphamide	9 (3)	8 (4.5)	1 (0.82)	**0.03**
Sulfasalazine	2 (0.7)	1 (0.6)	1 (0.82)	0.83
Azathioprine	40 (13.3)	31 (17.3)	9 (7.4)	**0.003**
Leflunomide	6 (2)	4 (2.2)	2 (1.6)	0.72
Rituximab	17 (5.6)	14 (7.8)	3 (2.5)	**0.048**

Note: Bold text indicates statistically significant values ($p < 0.05$).
Abbreviations: ALT, alanine transaminase; AST, aspartate transferase; C3, complement 3; C4, complement 4; ESR, erythrocyte sedimentation rate; F:M, female: male; RF, rheumatoid factor; SUA, serum uric acid; TLC, total leucocyte count.

Table 2 Characteristics of the Primary Sjögren's Syndrome Patients with and Without Double Anti-SSA and Anti-SSB Positivity

Parameter	Primary SS Patients (n=301)	Double Positive (n=126)	Single Positive (n=175)	*P value*
Sociodemographic data				
Age (years)	45.6±10.2	45.3±9.7	45.9±10.5	0.65
Gender F:M	265:36 (7.4:1)	108:18 (6:1)	157:18 (8.7:1)	0.3
Clinical data				
Disease duration (years)	4.6±4.03	5.04±4.2	4.3±3.9	0.22
Age at disease diagnosis (years)	41.4±9.3	40.6±8.7	42±9.7	0.19
Spontaneous abortions (n=265)	28 (10.6)	17 (13.5)	11 (6.3)	**0.045**
Hypertension	31 (10.3)	5 (4)	26 (14.9)	**0.001**
Diabetes	19 (6.3)	2 (1.6)	17 (9.7)	**0.001**
Clinical manifestations				
Dry eyes	283 (94)	118 (93.7)	165 (94.3)	0.61
Dry mouth	268 (89)	116 (92.1)	152 (86.9)	**0.045**
Enlarged parotid gland	133 (44.2)	46 (36.5)	87 (49.7)	0.052

(*Continued*)

Table 2 (Continued).

Parameter	Primary SS Patients (n=301)	Double Positive (n=126)	Single Positive (n=175)	*P value*
Lymphadenopathy	75 (24.9)	36 (28.6)	39 (22.3)	0.34
Mucocutaneous manifestations	103 (34.2)	49 (38.9)	54 (30.9)	0.16
Articular manifestations	121 (40.2)	66 (52.4)	55 (31.4)	**<0.0001**
Pulmonary manifestations	58 (19.3)	24 (19.04)	34 (19.4)	0.89
Cardiac manifestations	23 (7.6)	4 (3.2)	19 (10.9)	**0.007**
Gastrointestinal manifestations	54 (17.9)	20 (15.9)	34 (19.4)	0.35
Renal manifestations	21 (7)	6 (4.8)	15 (8.6)	**0.04**
Neurological manifestations	73 (24.3)	28 (22.2)	45 (25.7)	0.4
Fibromyalgia syndrome	16 (5.3)	13 (10.3)	3 (1.7)	**0.001**
Laboratory data				
Hemoglobin (g/dl)	11.04±1.4	11.3±1.2	10.8±1.4	**0.006**
TLC ($x10^3/mm^3$)	6.03±2.2	6±2	6.1±2.4	0.73
Platelets ($x10^3/mm^3$)	246.2±87.3	265.2±80.1	232.7±89.9	**0.006**
ESR ($mm/1^{st}$ hr)	45.2±24.9	40.3±22.6	48.7±25.9	**0.012**
Creatinine (mg/dl)	1.06±0.91	1.08±1.01	1.04±0.84	0.76
AST (U/L)	25.8±14.3	25.9±12.1	25.6±15.7	0.88
ALT (U/L)	30.3±21.3	29.2±15.4	31±24.6	0.56
SUA	5.3±1.5	4.87±1.89	5.38±1.46	0.46
ANA	179 (46.9)	95 (75.4)	84 (48)	**<0.0001**
RF	145 (48.2)	77 (61.1)	68 (38.9)	**<0.0001**
Low C3	18 (6)	10 (7.9)	8 (4.6)	0.17
Low C4	68 (22.6)	51 (40.5)	17 (9.7)	**<0.0001**
Therapeutic data				
Corticosteroids	82 (27.2)	40 (31.7)	42 (24)	**<0.0001**
Methotrexate	80 (26.6)	43 (34.1)	37 (21.1)	**0.003**
Antimalarials	163 (54.2)	75 (59.5)	88 (50.3)	0.06
Cyclophosphamide	9 (3)	6 (4.8)	3 (1.7)	0.16
Sulfasalazine	2 (0.7)	1 (0.8)	1 (0.6)	0.82
Azathioprine	40 (13.3)	30 (23.8)	10 (5.7)	**<0.0001**
Leflunomide	6 (2)	2 (1.6)	4 (2.3)	0.67
Rituximab	17 (5.6)	11 (8.7)	6 (3.4)	0.049

Note: Bold text indicates statistically significant values ($p < 0.05$).

Abbreviations: ALT, alanine transaminase; AST, aspartate transferase; C3, complement 3; C4, complement 4; ESR, erythrocyte sedimentation rate; F:M, female: male; RF, rheumatoid factor; SUA, serum uric acid; ANA, antinuclear antibody; and TLC, total leucocyte count.

and anti-La antibodies. On the other hand, patients with a single positive antibody (either anti-Ro or anti-La) had a higher prevalence of cardiac and renal manifestations (p = 0.007, 0.04, respectively).

Discussion

In this multicenter cross-sectional study of 301 Egyptian patients with pSS, we identified distinct clinical and immunological phenotypes associated with ANA and anti-Ro/anti-La antibody profiles. ANA positivity (59.5% of patients) was significantly associated with higher anti-Ro and anti-La seropositivity (p=0.001 and p<0.0001, respectively), reduced sicca symptoms including dry eyes (p=0.04) and parotid gland enlargement (p=0.001), along with increased use of corticosteroids (p=0.017) and azathioprine (p=0.003). Patients with double-positive anti-Ro/anti-La antibodies (41.9%) demonstrated more frequent articular manifestations (p<0.0001), fibromyalgia (p=0.001), and complement C4 consumption (p<0.001) compared to single-positive patients, while showing lower prevalence of hypertension and diabetes (p=0.01 for both).

Immunological patterns are crucial in shaping the phenotypic expression of the disease at the time of diagnosis and can help physicians tailor personalized management strategies for patients with pSS during follow-up.[17] In the current study, 59.5% had ANA positive and revealed varied characteristics. The ANA-positive patients exhibited a clinical phenotype largely similar to that of ANA-negative patients, but they showed a higher rate of RF positivity and increased use of corticosteroids, primarily due to joint involvement.[18] Patients with positive ANA in pSS generally show elevated levels of inflammation and a greater risk of multi-organ damage. Additionally, as ANA titers rise, the degree of inflammation and the likelihood of multi-organ damage also increase.[19] Paradoxically, the ANA and double anti-Ro and anti-La positivity were protective against comorbidities (hypertension and diabetes).

A higher frequency of low C3 and C4 were present in those with ANA and double anti-Ro and anti-La positive. This may point to the meticulous need for in-depth investigations and prolonged follow up to ascertain that these cases were not missed early SLE or other CTD cases that were initially presented by pSS. In this work, the platelet level was higher in those with ANA and double anti-Ro/anti-La positivity. Primary SS can lead to secondary immune thrombocytopenia (ITP) and such subgroup showed lower lymphadenopathy and arthritis as well as higher platelet counts, more lymphopenia, elevated immunoglobulin G (IgG) levels, lower complement 3 (C3) levels, and decreased white blood cell and hemoglobin levels.[20]

Patients with SS were more frequently found to be ANA-positive.[21] ANA positivity is linked to a roughly 14-fold higher likelihood of having pSScompared to non-SS conditions. This suggests that patients experiencing significant dry eye symptoms and testing positive for ANA should undergo diagnostic testing for SS, even if their SSA or SSB results are negative.[22] The current findings demonstrated a reduced prevalence of dry eyes among ANA-positive patients. In agreement with our findings, there was no correlation observed between ANA and the dry eye parameters in a study conducted on 49 SLE patients with dry eye.[23] This could be explained by the more aggressive medications administered to the ANA positive group in our cohort.

In the current study, we found that the prevalence of positive anti-Ro and/or anti-La antibodies was significantly higher in ANA positive patients. ANA analysis is a crucial diagnostic tool for a variety of autoimmune rheumatic disorders.[24] Positive ANA with a titre exceeding>1/80 is usually associated with the presence of positive anti-Ro and anti-La antibodies in pSS. This indicates that individuals diagnosed with pSS with elevated ANA titre exceeding 1/80 are significantly associated with the existence of anti-extranuclear antibodies. Moreover, an ANA >1/80 exhibited a remarkable positive predictive value (91%) for the classification of individuals with pSS. Based on this finding, a patient with sicca symptoms, positive ocular tests, parotid scintigraphy, and positive ANA >1/80 can be defined as having pSS in the absence of concurrent systemic autoimmune disorders, even if Ro/La antibodies are negative.[25]

In this cohort, the administration of corticosteroids and azathioprine was also statistically significantly higher in patients with positive ANA. It is reported that pSS patients with ANA have more severe and earlier glandular and extra-glandular disease and required more corticosteroids and immunosuppressive treatment than patients with negative ANA.[26]

In this work, 41.9% had double positive anti-Ro and anti-La and revealed varied characteristics. Patients with isolated La/SSB antibodies represent a small subgroup within the SS population, exhibiting a systemic SS phenotype marked by a notable frequency of active disease in most clinical European League Against Rheumatism Sjogren syndrome disease

activity index (ESSDAI) domains but with a relative low frequency of the highest severe organ-specific involvements. Primary SS still remains the best clinical diagnosis for this subset of patients.[27] The presence of anti-Ro and anti-La antibodies may be associated with higher levels of inflammation but does not appear to raise the risk of organ damage.[19]

Anti-La/anti-SSB-positive pSS patients were younger at the time of diagnosis and more frequently exhibited a range of symptoms, higher levels of other antibodies, and greater B-cell activation compared to anti-SSB-negative patients. They also required glucocorticoids and immunosuppressants more often, suggesting that the anti-SSB-positive group had a more severe clinical phenotype.[28]

In the current study, the mean disease duration was 4.6 years with ANA positivity associated with longer disease duration. Longer disease duration in pSS patients correlates with increased prevalence of sicca symptoms, fatigue, and arthralgia and higher positivity of autoantibodies associated with pSS. However, the prevalence of interstitial lung disease (ILD) and leukopenia did not correlate with disease duration after matching for age at disease onset.[29]

According to the geolocation across the country, there was a significant difference in age at disease diagnosis as the highest was for a patient from Aswan and the least from Giza. Highest autoantibodies, double anti-Ro and anti-La, ANA and RF positivity were in Minia. Geolocation and ethnicity significantly influence the phenotypic presentation of pSS at the time of diagnosis.[30] However, disease phenotype is also shaped by geographical origin, which serves as a risk factor for systemic disease activity.[4] A north-south gradient was observed, with a lower frequency of ocular involvement—such as dry eyes and abnormal ocular test results—in northern regions of Europe and Asia compared to southern regions. In America and Asia, northern countries showed higher rates of ANAs, while in Europe, northern countries had the lowest prevalence of ANAs and Ro/La antibodies.[30]

The age at diagnosis significantly impacts the key phenotypic characteristics of pSS and should be regarded as crucial. It not only guides the development of a personalized diagnostic approach but also requires careful consideration when interpreting diagnostic test results, immunological parameters, and assessing potential internal organ involvement at diagnosis.[31] In patients with pSS, the mean age at diagnosis was 50.1±13.1 years.[32] The mean age at disease diagnosis in our cohort was 41.4 years. In a cohort including 534 Sjögren's disease patients the median age was 54 years.[33] The onset of pSS occurs even before the age of 40 among Saudi citizens.[5] Additionally, pSS was diagnosed a mean of 7 years earlier in black/African-American compared with white patients.[30]

Middle-aged females are typically affected by pSS. However, the disease may occur in male patients and in females during their childhood/adolescence or in the elderly.[34] The majority of patients in the present study were female, exhibiting a female to male ratio of 7.4:1. In a big data study on 10,500 pSS patients from 22 countries, 93% were female.[17] Recognizing the influence of sex differences on SS can improve treatment strategies and disease prognosis.[35] Sex hormones, particularly estrogens and androgens, are highly influential, and maintaining a proper balance of these hormones is vital for ensuring the homeostasis of acinar cells in the lacrimal and salivary glands.[35] Additionally, chromosomes play a significant role in the sex-based differences observed in SS.[36] The gut microbiota also contributes to the sex-related differences seen in SS.[35]

The most common subjective presenting features at the time of the diagnosis were dry mouth (94.5%) and dry eye (91.3%).[32] In this study, dry eyes and mouth were remarkably reported. Dry eye and enlarged parotid glands were significantly present in ANA negative patients. Regarding systemic manifestations, our results revealed significant percentage with systemic manifestations. Indeed, over 25% of patients with pSS may experience systemic manifestations not currently captured by the ESSDAI. These include a broad range of cardiovascular, digestive, pulmonary, neurological, ocular, skin, and urological symptoms, which expand the systemic phenotype of the disease. However, the occurrence of each of these non-ESSDAI features is generally low, with the exception of Raynaud's phenomenon.[37]

Articular manifestation was one of the most common (40.2%) reported extraglandular manifestations in our cohort. Symmetrical polyarthritis was the most common clinical manifestation of pSS patients and usually associated with ESSDAI score.[38] A study of 355 patients revealed that strongly positive RF and anti-CCP levels, kidney involvement, and anti-Ro/SS-A positivity significantly increased the risk of RA, while anti-La/SS-B positivity appeared to play a protective role.[39] This study revealed pulmonary manifestations in about one fifth (19.3%) of the study population. High disease activity at the onset of pSS increases the risk of developing interstitial lung disease, highlighting the need for close monitoring and raising the possibility that immunomodulatory treatments could help prevent ILD.[40]

Identifying the neurological and psychiatric features of Sjögren's syndrome (SS) can aid in earlier diagnosis and result in improved clinical outcomes.[41] About one quarter (24.3%) of our study patients reported neurological manifestations. A significant proportion of our cohort reported gastrointestinal and hepatic manifestations. A causal relationship between SS and gastroesophageal reflux disease (GERD) has been confirmed where GERD is a risk factor for SS, while SS does not affect GERD.[42] An association was found between autoimmune liver disease (AILD) and SS.[43]

This multicenter study provides the first comprehensive characterization of ANA and anti-Ro/anti-La antibody profiles in Egyptian pSS patients, utilizing a large, nationally representative cohort (n=301) from 16 centers. Key strengths include standardized data collection through the ECR pSS database, rigorous phenotyping, and harmonized statistical analyses. However, the cross-sectional design limits causal interpretations, and potential recruitment bias from tertiary centers may affect generalizability to milder community cases. While we excluded overlapping autoimmune diseases to ensure cohort homogeneity, this restricts direct comparisons to other pSS populations. Future longitudinal studies should track disease progression and treatment responses in this cohort. We recommend incorporating genomic biomarkers and establishing standardized autoantibody assays across centers to improve diagnostic precision. The ECR commits to expanding this research through salivary gland imaging, proteomics, and collaborations with regional consortia to elucidate ethnic variations in pSS. These efforts will inform the development of tailored Egyptian clinical guidelines and a national pSS registry to optimize patient care and resource allocation.

Conclusion

Egyptian patients with pSS exhibit distinct clinical and laboratory phenotypes based on their anti-Sjögren autoantibody profiles (ANA, anti-Ro, and anti-La). These findings underscore the critical role of autoantibody profiling in predicting disease manifestations and guiding personalized management in Egyptian pSS patients. The study highlights the need for population-specific research to address potential ethnic variations in pSS expression and optimize therapeutic strategies.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that they have no conflicts of interest in this work.

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