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Sex Difference in Primary Sjögren Syndrome

A Medical Records Review Study

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Objectives: The aim of this study was to study clinical and biological differences between men and women with primary Sjögren syndrome (pSS) in China and perform a literature review to confirm if the clinical phenotypes are affected by sex in patients with pSS.

Methods: Data from 961 patients with pSS treated at a tertiary hospital in China between January 2013 and March 2022 were analyzed based on medical records. Clinical characteristics, including disease manifestations and serological parameters of the disease, were compared between men and women with pSS using the Mann-Whitney U test and χ^2 test.

Results: This study included 140 (14.6%) men and 821 (85.4%) women with pSS. Women with pSS demonstrated a higher prevalence of dry mouth, dry eyes, arthralgia, and dental caries ($p < 0.05$); higher erythrocyte sedimentation rate and immunoglobulin M levels ($p < 0.05$); higher prevalence of leukopenia, neutropenia, anemia, low complement 3, and low complement 4 ($p < 0.05$); and higher titers of antinuclear antibody, anti-Sjögren syndrome A, anti-Ro52, and rheumatoid factor positivity ($p < 0.05$) than men, whereas men with pSS had a higher prevalence of parotid enlargement and interstitial lung disease ($p < 0.05$).

Conclusions: Women with pSS are associated with more dryness, cytopenia, hypocomplementemia, and autoantibody positivity. Although men with pSS probably have lighter sicca symptoms and lower immunoactivity and serologic responses, regular monitoring of interstitial lung disease in men is vital.

Key Words: Sjögren syndrome, sex differences, clinical characteristics, autoantibodies, interstitial lung disease

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Primary Sjögren syndrome (pSS) is a systemic autoimmune disease characterized by B-cell hyperactivity and lymphocytic infiltration of the exocrine glands, leading to sicca symptoms such as xerostomia and xerophthalmia.[1] Primary Sjögren syndrome affects 0.3–1 per 1000 people in the general population and predominantly occurs in middle-aged women, but is also observed in children, men, and older adults. The female-to-male sex ratio in the incidence data is 9:1, and the prevalence ratio is 10.72:1.[2] The spectrum of the disease extends from a benign glandular disorder to aggressive systemic involvement, occurring in approximately 30%–40% of patients with pSS, including pulmonary and hematological.[3]

Genetic background, environmental factors, and demographic characteristics such as sex affect the phenotypic and severity of pSS. The male sex is a risk factor for pSS with interstitial lung disease (ILD), and it takes a shorter time for pSS to develop into lymphoma in men.[4,5] Furthermore, men with pSS have a significantly greater mortality risk, which is 3 times higher than that in women.[6,7] Consequently, more attention should be paid, and individualized therapeutic strategies should be formulated based on the specific clinical phenotype of pSS in men.

To date, some studies have attempted to explore the clinical phenotypes of pSS in patients of different sexes but have not reached a clear consensus.[8–19] Notably, the frequency of autoantibody positivity in men and women with pSS has been widely debated and even came to diametrically opposite conclusions.[8,9,13,18] Hematological abnormalities, as a common systemic involvement of pSS, have received insufficient attention in previous studies. Moreover, information regarding sex differences in the clinical phenotypes of pSS in Asia, especially China, is rather limited. The only study conducted in China lacked a comprehensive illustration of the clinical variables in pSS to reveal the phenotypes of Chinese male population.[16] These findings indicate that the influence of sex on clinical phenotypes is unclear in patients with pSS, especially in the Chinese population. Therefore, we conducted this medical records review study and literature review to further identify the clinical and biological differences between men and women with pSS in China to inform clinical practice.

METHODS

Study Population

The medical records of 961 patients with pSS were reviewed for this study. All the patients were treated at the China-Japan

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This study was approved by the Clinical Research Ethics Committee of the China-Japan Friendship Hospital (no. 2021-144-K102). The need for informed consent was waived because the data sets were anonymized.

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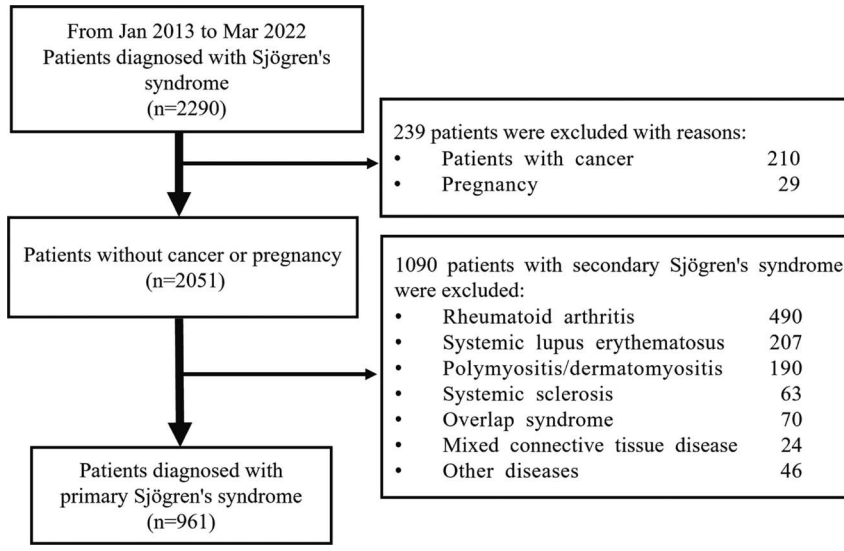

FIGURE 1. Flowchart for patient selection.

Friendship Hospital between January 2013 and March 2022 (Fig. 1). All of patients fulfilled the 2002 revised American-European classification criteria[20] or the 2016 American College of Rheumatology/European League Against Rheumatism classification criteria[21] for pSS. Patients with secondary SS, all kinds of cancer, or pregnancy were excluded. This study was approved by the Clinical Research Ethics Committee of the China-Japan Friendship Hospital (2021–144-K102). Informed consent was waived because the data were devoid of personal information.

Data Collection

Clinical data were retrieved from the medical records of eligible pSS patients and the hospital information system. The following data were collected: demographics (sex, age, and disease duration), clinical manifestations, laboratory findings, and histopathological examinations of minor salivary gland (MSG) biopsies. All the data were collected at the time of disease diagnosis.

The age at diagnosis of pSS was defined as the age at which the study participants were diagnosed with Sjögren syndrome, whereas the age at onset was defined as the age at the first appearance of disease-associated manifestations. Disease duration was defined as the timespan between pSS onset and diagnosis. An abnormal Schirmer I test result was defined as a result of ≤5 mm/5 min. Laboratory indicators contained serological and hematological parameters, including a full blood count; erythrocyte sedimentation rate (ESR); immunoglobulin G (IgG), IgA, IgM, complement 3 (C3), and complement 4 (C4); and titers of antinuclear antibody (ANA), anti-Sjögren syndrome A (anti-SSA) antibody, anti-Sjögren syndrome B (anti-SSB) antibody, anti-Ro52 antibody, antiribonucleoprotein (anti-RNP) antibody, anticentromere protein B (anti-CENPB) antibody, and rheumatoid factor (RF). Interstitial lung disease was examined using high-resolution computed tomography, assessed by 2 experienced radiologists, and eventually diagnosed by clinical doctors.

All data tests were performed using commercial techniques standardized at the hospital. ANA was determined by indirect immunofluorescence of HEp-2 cells, and a titer of ≥1:160 was defined as positive. Commercial immunoblotting kits were used to determine the titers of anti-SSA and other autoantibodies. An immunoturbidimetric assay determined the RF titers, and the levels >20 IU/mL were considered positive. Leukopenia was defined as white blood cell count $<4.00 \times 10^9$/L, neutropenia as neutrophil count $<1.5 \times 10^9$/L, lymphopenia as lymphocyte count $<0.8 \times 10^9$/L, anemia as hemoglobin <110 g/L, and thrombocytopenia as platelet count $<100 \times 10^9$/L. Elevated ESR was defined at a value of >20 mm/h. Hypergammaglobulinemia was defined as IgA >3.78 g/L, IgG >16.2 g/L, or IgM >2.63 g/L. Low C3 and C4 levels were defined by individual complement levels of <0.7 and <0.16 g/L, respectively. All pathological diagnoses of MSG biopsies were determined by pathologists at the hospital. A positive MSG biopsy was defined by focal lymphocytic sialadenitis with a focus score of ≥1. A focus score was defined as >50 lymphocytes per 4 mm^2 of glandular tissue.[20]

Statistical Analysis

Data analysis was performed using the SPSS software (Version 20.0). Descriptive statistics were used to define participants' characteristics. Frequencies and percentages were used to summarize the categorical data. The Shapiro-Wilk test was conducted to determine whether the data were normally distributed. Continuous data were reported as medians with its interquartile ranges (IQRs) for any nonnormally distribution. For statistical comparisons of categorical variables between groups, the χ^2 test for 2 × 2 contingency tables and Fisher exact test were used. The Mann-Whitney *U* test was used to analyze numerical variables. A 2-sided *p* value of <0.05 was considered statistically significant.

RESULTS

Demographic Characteristics of Men and Women at the Time of pSS Diagnosis

A total of 961 patients with pSS were included in this study, of whom 821 were women (85.4%) and 140 were men (14.5%; Table 1). The female-to-male sex ratio was approximately 6:1. Among the basic characteristics, the median age at the onset of pSS was 53.0 (IQR, 42.0–62.0) years, the median age at diagnosis was 58.0 (IQR, 49.0–66.0) years, and the median duration of pSS was 36.0 (IQR, 10.0–96.0) months. Men with pSS were significantly older at onset, with a median age of 59.0 (IQR, 52.75–67.0) years in men and 51.0 (IQR, 41.0–60.0) years in women ($p < 0.001$). Similarly, men with pSS had a significantly older age at diagnosis than women (63.5 [54.0–70.0] vs 58.0

TABLE 1. Differences in Clinical Manifestations and Laboratory Characteristics Between Men and Women With pSS

	Total (n = 961)	Men (n = 140)	Women (n = 821)	*p* value
Characteristics				
Age at onset, y	53.0 (42.0–62.0)	59.0 (52.75–67.0)	51.0 (41.0–60.0)	**<0.001**
Age at diagnosis, y	58.0 (49.0–66.0)	63.5 (54.0–70.0)	58.0 (49.0–65.0)	**<0.001**
Disease duration, mo	36.0 (10.0–96.0)	14.0 (4.0–48.0)	48.0 (12.0–96.0)	**<0.001**
Clinical manifestations				
Dry mouth	822 (85.5)	111 (79.3)	711 (86.6)	**0.023**
Dry eyes	762 (79.3)	94 (67.1)	668 (81.4)	**<0.001**
Fatigue	474 (49.3)	61 (43.6)	413 (50.3)	0.141
Arthralgia	367/951 (38.6)	39/139 (28.1)	328/812 (40.4)	**0.006**
Schirmer I test ≤5 mm/5 min	879 (91.5)	128 (91.4)	751 (91.5)	0.986
Dental caries	347/904 (38.4)	29/125 (23.2)	318/779 (40.8)	**<0.001**
Parotid enlargement	132/959 (13.8)	27 (19.3)	105/819 (12.8)	**0.040**
ILD	371 (38.6)	87 (62.1)	284 (34.6)	**<0.001**
Laboratory findings				
Leukocyte, $\times 10^9$/L	5.11 (3.92–6.67)	5.84 (4.73–7.67)	4.95 (3.81–6.59)	**<0.001**
Neutrophil, $\times 10^9$/L	2.99 (2.11–4.25)	3.50 (2.78–4.81)	2.88 (2.03–4.09)	**<0.001**
Lymphocyte, $\times 10^9$/L	1.50 (1.12–1.89)	1.58 (1.15–2.04)	1.48 (1.12–1.86)	0.082
Hemoglobin, g/L	125.0 (114.0–135.0)	137.5 (125.0–147.8)	123.0 (112.0–132.0)	**<0.001**
Platelet, $\times 10^9$/L	192.0 (150.5–241.0)	186.0 (150.0–232.0)	194.0 (151.0–242.5)	0.623
ESR, mm/h	19.0 (10.0–37.8)	16.0 (7.5–36.5)	20.0 (11.0–38.0)	**0.034**
Immunoglobulin G, g/L	15.60 (12.40–20.10)	15.65 (11.95–18.83)	15.50 (12.50–20.30)	0.206
Immunoglobulin A, g/L	2.83 (2.00–3.86)	2.93 (1.98–3.86)	2.82 (2.00–3.86)	0.844
Immunoglobulin M, g/L	1.05 (0.72–1.56)	0.89 (0.63–1.40)	1.08 (0.74–1.59)	**0.003**
C3, g/L	0.85 (0.72–0.97)	0.88 (0.79–0.99)	0.83 (0.71–0.96)	**0.005**
C4, g/L	0.18 (0.15–0.23)	0.20 (0.16–0.25)	0.18 (0.14–0.22)	**0.003**
ANA titers ≥1:160	567/934 (60.7)	57/134 (42.5)	510/800 (63.7)	**<0.001**
Positive anti-SSA	630/934 (67.5)	58/134 (43.3)	572/800 (71.5)	**<0.001**
Positive anti-SSB	254/934 (27.2)	30/134 (22.4)	224/800 (28.0)	0.177
Positive anti-Ro52	533/934 (57.1)	51/134 (38.1)	482/800 (60.3)	**<0.001**
Positive anti-RNP	66/934 (7.1)	9/134 (6.7)	57/800 (7.1)	0.864
Positive anti-CENPB	69/934 (7.4)	2/134 (1.5)	67/800 (8.4)	**0.005**
Positive RF[a]	385/888 (43.4)	36/117 (30.8)	349/771 (45.3)	**0.003**
Positive MSG biopsy[b]	520/544 (95.6)	96/101 (95.0)	424/443 (95.7)	0.770

Bold values indicate statistically significant findings ($p < 0.05$).

All values are presented as n (%) or median (IQR).

[a]Positive RF > 20 IU/mL.

[b]Positive MSG biopsy was defined by focal lymphocytic sialadenitis with a focus score of ≥1 focus/4 mm^2.

[49.0–65.0], $p < 0.001$). Furthermore, men with pSS had a significantly shorter disease duration than women (14.0 [4.0–48.0] vs 48.0 [12.0–96.0], $p < 0.001$).

Differences in Clinical Manifestations Between Men and Women With pSS

As shown in Table 1, dry mouth (85.5%) was a common manifestation in patients with pSS. On ocular evaluation, 79.3% of patients with pSS complained of dry eyes, and the majority (91.5%) of patients demonstrated abnormal Schirmer I test results. The percentages of fatigue, arthralgia, dental caries, parotid enlargement, and ILD in included pSS patients were 49.3%, 38.6%, 38.4%, 13.8%, and 38.6%, respectively.

Women with pSS had a significantly higher proportion of dry mouth (86.6% vs 79.3%, $p = 0.023$), dry eyes (81.4% vs 67.1%, $p < 0.001$), arthralgia (40.4% vs 28.1%, $p = 0.006$), and dental caries (40.8% vs 23.2%, $p < 0.001$) than men. However, the proportion of ILD in men with pSS was approximately twice that in women, and this difference was statistically significant (62.1% vs 34.6%, $p < 0.001$). Men with pSS had a significantly higher proportion of parotid enlargement (19.3% vs 12.8%, $p = 0.040$) than women. No significant difference was detected between men and women with pSS regarding abnormal Schirmer I test results and parotid enlargement (Table 1).

Laboratory Characteristics in Men and Women With pSS

Autoantibody profiles were analyzed in a sex-specific manner (Table 1), which revealed that 60.7% of patients with pSS had ANA titers of ≥1:160. Anti-SSA, anti-SSB, anti-Ro52, anti-RNP, anti-CENPB, and RF positivity were observed in 67.5%, 27.2%, 57.1%, 7.1%, 7.4%, and 43.4% of included patients, respectively. Minor salivary gland biopsies were performed in 544 (56.6%) of pSS patients, and 95.6% of them had positive findings,

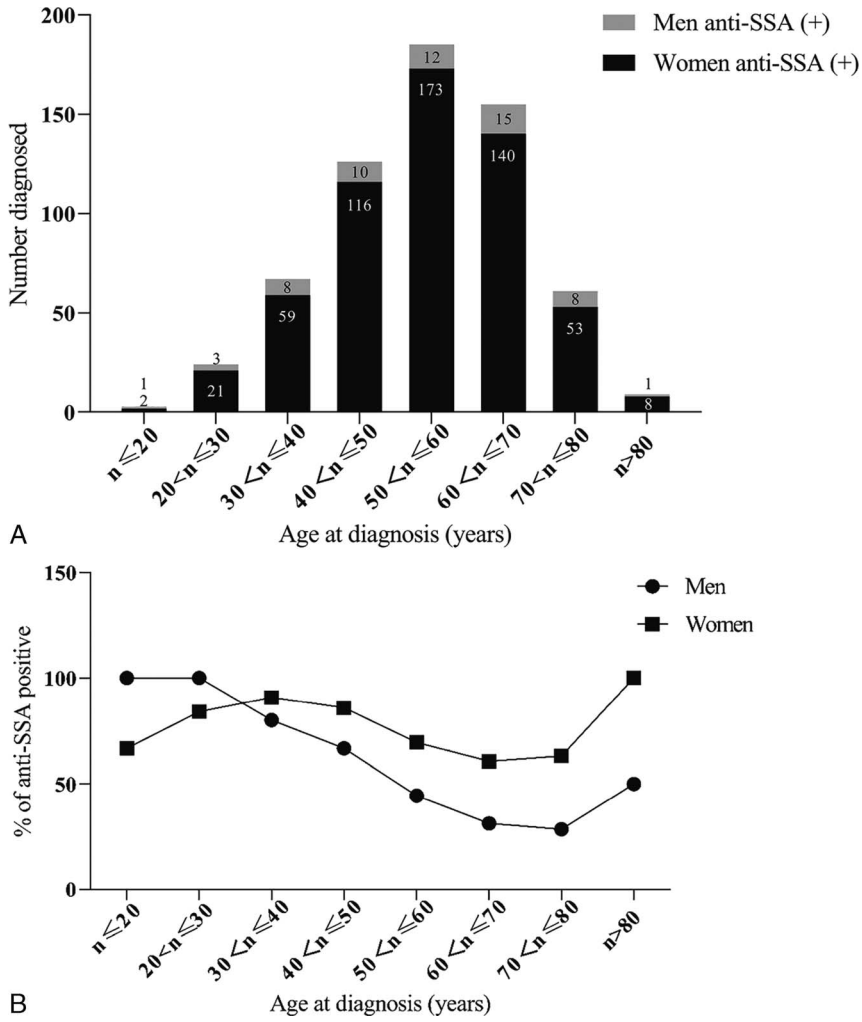

FIGURE 2. A, The number of male and female pSS patients with positive anti-SSA in different age intervals. B, Percentage of anti-SSA positivity in male and female patients with pSS in different age intervals.

with no significant difference in the proportion of positive results between women and men.

Women with pSS had a significantly higher autoantibody positivity rate, including ANA (63.7% vs 42.5%, $p < 0.001$), anti-SSA (71.5% vs 43.3%, $p < 0.001$), anti-Ro52 (60.3% vs 38.1%, $p < 0.001$), and anti-CENPB (8.4% vs 1.5%, $p = 0.005$) than men. Rheumatoid factor positivity was observed in 45.3% of women and 30.8% of men with pSS ($p = 0.003$).

According to the stratification of women and men with pSS showing anti-SSA positivity based on age at diagnosis, the number of women with anti-SSA positivity increased with age at diagnosis until 60 years of age (Fig. 2A). However, the number of men with pSS showing anti-SSA positivity did not significantly increase with age. Furthermore, the percentage of anti-SSA positivity was analyzed, which revealed that the trend was similar in both men and women (Fig. 2B). In the 20–30-year range, the percentage of men with pSS showing anti-SSA positivity started to decline and did so steadily until the 70–80-year range. Correspondingly, the percentage of women showing anti-SSA positivity decreased from the 30–40-year range until the 60–70-year range. Interestingly, beyond the 30–40-year range, the data indicated a consistently lower percentage of men with pSS showing anti-SSA positivity than that of women.

Significant differences were also detected in many other laboratory indicators between men and women with pSS (Table 1). Men with pSS had higher leukocyte counts (5.84 [4.73–7.67] $\times$ 10^9/L vs 4.95 [3.81–6.59] $\times$ 10^9/L, $p < 0.001$), neutrophil counts (3.50 [2.78–4.81] $\times$ 10^9/L vs 2.88 [2.03–4.09] $\times$ 10^9/L, $p < 0.001$), and hemoglobin levels (137.5 [125.0–147.8] g/L vs 123.0 [112.0–132.0] g/L, $p < 0.001$) than women. Furthermore, women with pSS had a higher prevalence of leukopenia (28.8% vs 10.7%, $p < 0.001$), neutropenia (8.9% vs 2.9%, $p = 0.015$), and anemia (20.8% vs 8.6%, $p = 0.001$; Fig. 3A). Comparisons of lymphocyte and platelet counts between men and women with pSS did not show any statistically significant differences. In addition, the prevalence of lymphopenia and thrombocytopenia was similar between men and women with pSS.

Significant differences were observed in the immunological parameters between men and women with pSS (Table 1). Women with pSS demonstrated significantly higher ESR (20.0 [11.0–38.0] mm/h vs 16.0 [7.5–36.5] mm/h, $p = 0.034$) and IgM levels (1.08 [0.74–1.59] g/L vs 0.89 [0.63–1.40] g/L, $p = 0.003$) than men. Moreover, women with pSS had significantly lower levels of C3 (0.83 [0.71–0.96] g/L vs 0.88 [0.79–0.99] g/L, $p = 0.005$) and C4 (0.18 [0.14–0.22] g/L vs 0.20 [0.16–0.25] g/L, $p = 0.003$), but higher proportions of low C3 (22.7% vs 14.1%, $p = 0.025$)

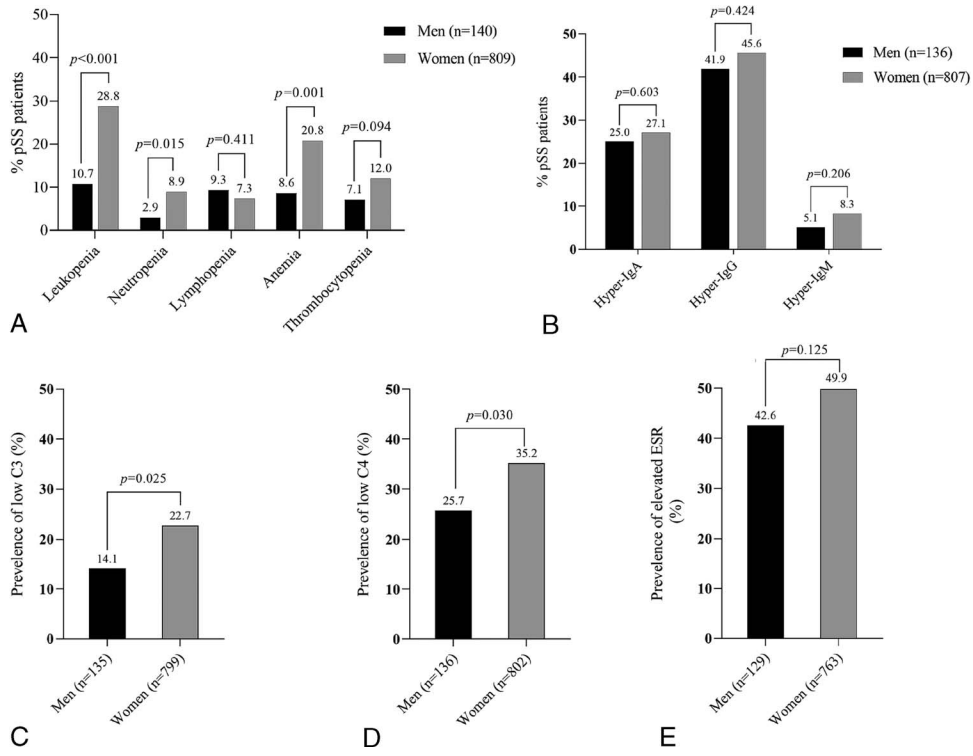

FIGURE 3. Comparisons of the prevalence in men and women pSS patients who had abnormal serological and hematological parameters. A, Prevalence of cytopenias in men and women with pSS. B, Prevalence of hyperglobulinemia in men and women with pSS. C and D, Prevalence of hypocomplementemia in men and women with pSS. E, Prevalence of elevated ESR in men and women with pSS. Leukopenia: white blood cell counts <4.00 × 109/L; neutropenia: neutrophil counts <1.5 × 109/L; lymphopenia: lymphocyte counts <0.8 × 109/L; anemia: hemoglobin concentrations <110 g/L; thrombocytopenia: platelet counts <100 × 109/L. Hyper-IgA: immunoglobulin A > 3.78 g/L; hyper-IgG: immunoglobulin G > 16.2 g/L; hyper-IgM: immunoglobulin M > 2.63 g/L. Low C3: complement 3 < 0.7 g/L. Low C4: complement 4 < 0.16 g/L. Elevated ESR: erythrocyte sedimentation rate >20 mm/h.

and low C4 (35.2% vs 25.7%, $p = 0.030$; Figs. 3C, D) levels than men. However, differences in other laboratory findings, including IgA and IgG levels, and prevalence of hyperglobulinemia and elevated ESR were not statistically significant between men and women with pSS (Figs. 3B, E).

Literature Review

To date, 12 studies have described sex differences in the clinical phenotypes of pSS but presented inconsistent results (see Table, Supplemental Digital Content 1, http://links.lww.com/RHU/A537, which demonstrates characteristics of relevant previous studies).[8–19] Among these studies, 3 were conducted in the United States,[8,9,11] 7 in European countries,[10,12–15,17,18] and only 2 were conducted in Asian men with pSS (Korea and China).[16,19] In 1986, Molina et al[8] first described the clinical, serologic, and immunogenetic features in pSS among 36 men with pSS. A prospective study[18] conducted in Sweden in 2017, with a sample size of 967 patients, was the largest of its kind.

In terms of clinical manifestations, only 2 studies conducted in Asia have reported that men with pSS had a significantly lower percentage of sicca syndrome than women[16,19]; none of the remaining found significant sex differences in glandular manifestations, including salivary gland swelling. In addition, these studies have focused on multiple extraglandular manifestations in men and women with pSS. Two studies showed that men with pSS had less articular involvement than women,[10,12] whereas 2 other studies reported the opposite results.[14,16] No differences in the prevalence of pulmonary involvement between men and women with pSS were reported in studies conducted before 2017.[8–16] However, 3 subsequent studies demonstrated a higher frequency of ILD in men with pSS than in women.[17–19]

Of the 7 studies that reported sex differences in hematological abnormalities of pSS, 3 reported a lower frequency of leukopenia in men,[15,16,19] 2 reported a higher frequency of lymphoma in men,[18,19] and 3 did not find any significant differences.[8,9,17] Regarding immunological parameters, Molina et al[8] first revealed that men with pSS had a lower prevalence of autoimmune markers, including RF and anti-SSA antibody, than women. Later, 4 studies reported similar conclusions.[10,11,16,19] In contrast, a 2004 retrospective study[13] conducted in Spain reported a higher frequency of RF in men with pSS, and a 2017 prospective study[18] reported more frequent positivity for ANA, anti-SSA, and anti-SSB antibodies in men with pSS than in women. Interestingly, the other 5 studies found no significant difference in the frequency of positive autoantibodies and RF between men and women with pSS.[9,12,14,15,17] In summary, previous relevant studies have indicated that the results regarding sex differences in the clinical manifestations and laboratory findings of pSS are controversial.

DISCUSSION

To the best of our knowledge, this medical records review study had the largest sample size of men to survey sex differences in the clinical characteristics of pSS patients in China. It has been widely established that women are more likely to develop pSS than men. The genetic and epigenetic mechanisms (including X chromosome inactivation, sex chromosome aneuploidy, and

microchimerism) and sex hormone regulation of inflammation result in distinct immunopathological differences between male- and female-predominant autoimmune diseases.[22,23] Clinical phenotypes across divergent sex-specific preferences may indicate the underlying pathophysiological mechanisms of pSS. Although this issue has been explored in past studies,[8–19] the disease pattern is not fully understood due to the controversial results. The major findings of this study are (*a*) women with pSS demonstrated more dryness; arthralgia; dental caries; higher rates of ANA, anti-SSA, anti-Ro52, and RF positivity; higher IgM levels and ESR; and higher prevalence of cytopenia and hypocomplementemia; (*b*) a consistently higher proportion of women with pSS showed anti-SSA positivity beyond the 30–40-year range than did men; and (*c*) men with pSS demonstrated more parotid enlargement and ILD and higher leukocyte counts, neutrophil counts, hemoglobin levels, C3 levels, and C4 levels than women.

Differences in Clinical Manifestations

Except for 2 Asian studies,[16,19] the majority of previous studies found no differences in glandular presentation between men and women with pSS. In our study, women complained more about dry mouth and dry eyes, possibly because estrogen contributed to the increasing rates of death of the tear duct and salivary gland cells, resulting in xerophthalmia and xerostomia after menopause.[23] A nested case-control study determined that Whites were more likely to have xerostomia than Asians,[24] which may be a reason why previous studies from European and American countries did not detect sex differences in xerostomia.[8–10,12–15,17,18] In terms of extraglandular manifestations, our study indicated that the female sex was associated with a higher prevalence of arthralgia and dental caries. In previous studies, Raynaud phenomenon, fatigue, fibromyalgia, depression, and thyroiditis were found to occur more frequently in women with pSS than in men.[10,11,13,14] However, sex differences in articular involvement have been inconsistent,[10,12,14,16] which may result from differences in discriminative methods, including patient-described symptoms or radiographic indications of arthritis.

Bournia et al[25] reported that more severe exocrine gland dysfunction and a higher prevalence of extraglandular manifestations in women with pSS might be correlated with more frequent Ro/La antibody positivity. However, Billings et al[24] indicated that anti-SSA and anti-SSB antibodies were not significant predictors of xerostomia. Interestingly, parotid enlargement was more common in men with pSS than in women. Men with pSS were less likely to be screened for salivary gland function because of fewer complaints of dry mouth.[24] However, they reported a higher prevalence of parotid enlargement, suggesting that salivary gland function should be examined in men with suspected pSS.

Patients with pSS-associated ILD have been reported as having impaired quality of life and a higher risk of death.[26] In our study, up to 62.1% of men with pSS experienced ILD, and the prevalence is 1.8 times higher than that of women. Similarly, previous studies reported that men with pSS had more pulmonary involvement, including ILD.[17–19] All these suggested that men with pSS should be screened earlier and more intensively for pulmonary involvement than women. We searched for the reasons and underlying mechanisms of this male predominance in the literature; however, it has not yet been elucidated. It may be related to genetics, estrogen's protective effect, a higher smoking frequency in men, air pollution, or occupational exposure.[5,27] Furthermore, the frequency of ILD increased with the age at diagnosis,[28] and the fact that men with pSS were diagnosed at older ages than women was also one of the reasons. Its specific underlying mechanisms require further exploration. Of note, the timespan between onset to diagnosis in men with pSS was 1.2 years, significantly earlier than 4 years in women. Perhaps it could be speculated that some of them went to seek medical attention earlier due to the annoying symptoms such as dyspnea or cough, rather than sicca symptoms. Fortunately, none of the existing studies have found male preponderance in the involvement of other organs, except for pulmonary.

Differences in Laboratory Indicators

A previous study confirmed that estrogen can activate B cells, resulting in increased levels of autoantibodies, leading to a higher prevalence of autoimmune diseases in women than in men.[23] Consistent with this hypothesis, the influence of sex hormones on pSS has also been supported. In several studies, women with pSS generally demonstrated more immunological manifestations such as anti-SSA and RF positivity; however, men with pSS demonstrated lower biological activity.[8,9,16,19] Similarly, our study showed that women with pSS had higher proportions of ANA, anti-SSA, anti-Ro52, and RF positivity and higher IgM levels and ESR than men. In addition, women showed a consistently higher proportion of anti-SSA positivity beyond the 30–40-year range, which could rule out the effect of age on sex differences and testify that the postmenopausal lower doses of estrogen are still able to promote B-cell proliferation and autoantibody production after menopause in women.[23]

In contrast, 2 studies enrolling 1516 patients came to the opposite conclusion as they reported male predominance for autoantibodies in pSS.[13,18] One prospective study[18] had a large sample size and used long-term follow-up to assess serological parameters some years after diagnosis. Nevertheless, because autoantibodies can change with age or treatment[29] and men and women with pSS may have potentially different degrees of response to treatment, the credibility of male dominance of autoantibodies reported in that study requires further investigation. Notably, 4 previous studies[9,12,15,17] detected no significant sex differences in immunological characteristics. Racial differences resulting in susceptibility to pSS, sample size, and different detection methods and sensitivity to antibodies from different institutions may be the reasons for the inconsistencies noted between these studies.

Lower levels of C3 and C4 and a higher prevalence of low C3 and C4 were noted in women with pSS than that in men in our study, which was not reported in previous studies.[8–19] Previous studies demonstrated that hypocomplementemia in women with pSS may be associated with higher anti-SSA positivity and may herald adverse outcomes (lymphoma development and death),[30,31] which warrants attention from clinicians. Hemocytopenia was found in approximately 33% of patients with pSS,[32] and some studies have reported higher prevalence of lymphopenia and leukopenia but lower prevalence of thrombocytopenia in women.[15,16,18,19] Our study described that women with pSS presented more hematologic abnormalities, such as lower leukocyte counts, neutrophil counts, and hemoglobin levels, and correspondingly, a higher prevalence of leukopenia, neutropenia, and anemia, than men. Therefore, women with pSS should be alerted to the possibility of infection during disease surveillance.[33] Anti-SSA antibodies and RF may directly mediate the development of cytopenia,[30,34] which could be evidence that women with pSS have a higher frequency of autoantibody expression. Based on findings from most current studies, it appears reasonable to conclude that women with pSS have higher precedence for hematologic abnormalities and serologic hyperreactivity than men, indicating that sex can modulate serological manifestations of pSS.

Differences in Risk of Cancer and Death

Patients with pSS have a higher risk of developing lymphoma,[35] especially men.[18,19] Lymphadenopathy and parotid enlargement, which were more common in men, were considered lymphoma disease predictors,[19,35] and it takes less time for men to progress from pSS to lymphoma,[4] so clinicians need to be aware of signs of lymphoma in men earlier. Furthermore, pSS patients had an increased risk of other hematological malignancies (including multiple myeloma and leukemia) and solid tumors (including mouth and throat cancer, nonmelanoma skin cancer, liver cancer, lung cancer, prostate cancer, and kidney cancer).[36] Interestingly, the cancers mentioned previously have a higher incidence in men,[37,38] suggesting that sex may be a vital parameter in the increased risk of overall cancer in pSS patients. Therefore, men with pSS merit more monitoring for malignant tumors.

Of note, pSS patients also have an increased risk of death when compared with the general population. The standardized mortality ratio of men with pSS was more than one time that of women.[6] Phenotypes including the age at diagnosis over 50 years old, ILD, vasculitis, thrombocytopenia, low complements, and cryoglobulinemia were risk factors for mortality in pSS.[6,39] Therefore, deaths in women with pSS may be associated with a higher prevalence of hypocomplementemia and cryoglobulinemia,[40] indicating such patients should be given more surveillance. Similarly, older male pSS patients with ILD also require closer follow-up.

Limitations

There are several limitations to this study. First, this is a medical record review study. Our findings provide a better understanding of the influence of sex on clinical phenotypes in Chinese patients with pSS, but it does not mirror the general pSS patient population. Second, we could not analyze all clinical features of pSS because some data were missing in the medical records. Therefore, this study lack the exploration of sex differences in the involvement of some organs between men and women with pSS. In the future, multicenter longitudinal studies with long-term follow-up are warranted to support our findings.

CONCLUSIONS

The clinical phenotypes of pSS differ between women and men. Women with pSS had more dryness, cytopenia, low C3 and C4 levels, and autoantibodies positivity than men. Although men with pSS probably have lighter sicca symptoms and lower immunoactivity and serologic responses, regular monitoring of ILD in men is vital.

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