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Primary Sjögren Syndrome in Han Chinese

Clinical and Immunological Characteristics of 483 Patients

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Abstract: The epidemiological characteristics of Sjögren syndrome (SS) are significantly varied in different countries. We conducted the present study to survey the epidemiological characteristics of primary SS in China. We recruited 483 primary SS patients from 16 Chinese medical centers nationwide from January 2009 to November 2011 and assessed salivary and lacrimal gland dysfunction, organ involvement, and autoimmunity in these patients. The cohort included 456 women and 27 men (ratio, 17:1; mean age at onset, 42 ± 11 years; median age at diagnosis, 49 years; range, 41–56 years). Male patients showed a lower frequency of xerophthalmia (37.0% vs 60.7%) and a higher frequency of arthritis (40.7% vs 16.4%). Young-onset patients showed a higher frequency of low C3 levels (57.7% vs 36.3%) and pancytopenia (22.2% vs 8.8%). Patients with systemic involvement had a higher frequency of immunoglobulin A (IgA) (39.4% vs 22.5%) and immunoglobulin M (IgM) (12.4% vs 37.9%). Patients with pulmonary involvement had a higher parotid enlargement (21.4% vs 10.2%), purpura (12.1% vs 5.7%) and higher anti-La/SS-B (61.7% vs 41.8%), immunoglobulin G (IgG) (80.7% vs 64.6%) and IgA (48.9% vs 30.6%) levels. Patients with anti-Ro/SSA antibodies had more frequent exocrine gland symptoms and some extraglandular symptoms and immunological alterations. Compared with previous studies performed in other countries, SS patients in China showed particular clinical manifestation, systemic involvement, and immunological alterations.

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Abbreviations: ACR = American College of Rheumatology, ANA = antinuclear antibodies, CNS = central nervous system, CT = computed tomography, Ig = immunoglobulin, IgA = immunoglobulin A, IgM = immunoglobulin M, RF = rheumatoid factor, SS = Sjögren's syndrome.

INTRODUCTION

Primary Sjögren syndrome (SS) is an autoimmune disease that affects the exocrine glands and other parenchymal organs (ie, the kidney, lung, and liver), leading to dryness of the main mucosal surfaces and extraglandular manifestations.[1,2] The disease overwhelmingly affects middle-aged women, and some patients (approximately 5%–10%) develop lymphoma.[3] The prevalence of primary SS in China is approximately 0.33%

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to 0.77%, according to different criteria.[4] Recent studies have reported that the prevalence ranges from 0.05% to 0.23% in other countries.[5,6] Primary SS is associated with several immune abnormalities, of which antinuclear antibodies (ANAs) and increased immunoglobulin (Ig) levels are the most frequently detected; anti-Ro/SS-A is the most specific abnormality, and cryoglobulins and hypocomplementemia are the main prognostic markers. The histological hallmark is focal lymphocytic infiltration of the exocrine glands and other parenchymal organs.[7]

SS is a heterogeneous disease that has a wide spectrum.[8,9] The variability of its presentation may significantly delay its diagnosis after the onset of symptoms.[10,11] The presentation of SS may be significantly influenced by epidemiological characteristics, systemic involvement, or the immunological profile at diagnosis. Some researchers have analyzed such factors.[12,13] These studies have yielded different results, likely because of the small number of patients included and the different classification criteria used. We conducted the present study to characterize the clinical presentation of primary SS in a large cohort of Chinese patients and to define epidemiologic, clinical, and immunologic subsets of patients to facilitate earlier diagnosis for Chinese SS patients.

METHODS

Patients

We registered 483 consecutive patients from 16 Chinese medical centers nationwide from January 2009 to November 2011 who fulfilled the 2002 classification criteria for primary SS.[14] The following exclusion criteria were applied: chronic hepatitis C virus or human immunodeficiency virus infection and previous lymphoproliferative processes or associated systemic autoimmune diseases.

Heart involvement was indicated by persistently altered electrocardiographic examinations (with the exception of nodal tachycardia and bradycardia), and/or structural abnormalities detected by ultrasound. Pulmonary involvement was indicated by persistent cough and/or dyspnea with chronic diffuse interstitial infiltrates on X-rays, altered patterns on pulmonary function tests, and/or evidence of lung alveolitis or fibrosis in computed tomography (CT) scans. Nephropathy was defined as persistent proteinuria (>0.5 g/day), altered urine analysis (hematuria, pyuria, and red blood cell casts), a persistently elevated serum creatinine level (84 μmol/L), renal tubular acidosis, interstitial nephritis, or glomerulonephritis. Liver involvement was indicated by altered serum hepatic function test results (aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, and bilirubin) and/or evidence of altered bile ducts in imaging-based examinations (ultrasound, CT, or magnetic resonance imaging).

Immunological tests were performed using commercial techniques standardized at Peking Union Medical College Hospital (indirect immunofluorescence for ANA, ELISA for anti-Ro/La antibodies and Ig, nephelometry for rheumatoid factor [RF], and immunoturbidimetry for C3/C4); anti-Ro/SSA antibodies were tested using commercial ELISA kits that detected IgG, IgA, and IgM antibodies to the 60-kDa and 52-kDa forms of Ro. This study was approved by the Ethics Committee of the Chinese Academy of Medical Sciences, Peking Union Medical College Hospital and, subsequently, by each participating center. The study design conformed to current Chinese ethical standards.

Statistical Analyses

Descriptive data are presented as means ± standard deviation for continuous variables when the data were normally distributed or as M (P_{25}–P_{75}) when the data were non-normally distributed; numbers (%) are indicated for the categorical variables. Continuous variables were analyzed with Student *t* test in large samples of similar variance, or with the nonparametric Mann–Whitney *U* test for small samples. Categorical data were compared using the χ^2 or Fisher exact tests. A 2-tailed value of $P < 0.05$ indicated statistical significance. Multiple logistic regression was used in the univariate analysis, adjusted for the statistically significant variables ($P < 0.05$). Statistical analyses were performed with the 12.0 Stata/SE program (StataCorp LP, College Station, TX).

RESULTS

The patient cohort comprised 483 individuals, including 456 (94.4%) women and 27 (5.6%) men (female: male ratio, 17:1), with a mean age at onset of 41.7 ± 11.0 years (range, 14–77 years). The median age at diagnosis was 49 (41–56) years (range, 17–89 years). The median period of time from the first SS-related symptom to diagnosis was 12 (6–22) years (range, 0–65 years). There were 260 patients (85.8%) with positive salivary gland biopsies among 303 patients who were examined. The remaining patients with negative gland biopsies were diagnosed with SS due to positive anti-SSA and/or anti-SSB tests, as well as other SS-related symptoms (Table 1).

SS in Men

Among the 483 patients with primary SS, 27 (5.6%) were men. Men showed a lower frequency of xerophthalmia, leucopenia, erythrocyte sedimentation rate (ESR), RF positivity, and anti-La/SS-B positivity; in addition, arthritis was more prevalent in men compared with women by univariate analysis. Multivariate analysis identified xerophthalmia ($P = 0.007$) and arthritis ($P = 0.006$) as independent variables (Table 2).

Young-onset SS (Age at Diagnosis 35 Years or Younger)

Primary SS was diagnosed before age 35 years in 75 of 455 (5.3%) patients. Among the initial symptoms, sicca, saprodontia, arthritis, and xerophthalmia were observed less frequently. In addition, there was a higher prevalence of purpura and flaccid paralysis resulting from hypokalemia and pancytopenia, and high IgG levels and low C3 levels were found at diagnosis in patients 35 years old and younger compared with patients older than 35 years, according to univariate analysis. Multivariate analysis identified pancytopenia ($P = 0.04$) among the initial symptoms and low C3 levels ($P = 0.009$) as independent variables (Table 3).

Systemic Disease Involvement

In total, 355 patients had their hearts tested, and 61 (17.2%) showed abnormalities, including heart package effusion (36/309, 11.8%) and atrioventricular blockage (27/355, 8.1%). Of the 384 patients who took the lung test, 143 (29.6%) showed pulmonary injury, including interstitial lung disease (59/317, 18.6%), abnormal pulmonary function (35/297, 11.8%), pulmonary hypertension (29/274, 10.6%), multiple lung bullae (30/317, 9.5%), and pleural effusion (20/317, 6.3%). Of the 384 patients who took the renal test, 36 (7.5%) showed renal injury, including urine protein positive (31/483, 6.4%), renal tubular

TABLE 1. Demographic, Clinical, and Immunologic Features of 483 Chinese Patients With Primary SS

Variables at Protocol*	n = 483
Sex, male, n(%)	27 (5.6)
Age at onset, mean (SD), years	42 ± 11
Age at diagnosis, M (P_{25}–P_{75}), years	49 (41 ~ 56)
Interval time, M(P_{25}–P_{75}), years	12 (6 ~ 22)
Initial symptoms	
Sicca symptoms, n (%)	354 (73.3)
Parotid enlargement, n (%)	64 (13.3)
Saprodontia, n (%)	114 (23.6)
Purpura, n (%)	37 (7.7)
Flaccid paralysis due to hypokalemia	26 (5.4)
Fever	39 (8.1)
Articular involvement, n (%)	184 (38.1)
Hypocytosis, n (%)	52 (10.8)
Xerostomia, n (%)	373 (77.2)
Xerophthalmia, n (%)	292 (60.5)
Saprodontia, n (%)	261 (54.0)
Parotid enlargement, n (%)	98 (20.3)
Altered ocular tests, n (%)	404/419 (96.4)
Schirmer *I* test (≤5 mm in 5 min), n (%)	381/419 (90.9)
ocular dye positive, n (%)†	349/419 (83.3)
Altered oral tests, n (%)	393/467 (84.2)
WUSF (≤1.5 mL in 15 min)	337/467 (72.2)
Parotid sialography positive‡	341/467 (73.0)
Salivary scintigraphy positive§	329/467 (70.4)
Positive salivary gland biopsy, n (%)	260/303 (85.8)
Arthritis	86 (17.8)
Fever	64 (13.3)
Fatigue	64 (13.3)
Purpura, n (%)	46 (9.5)
Flaccid paralysis due to hypokalemia	29 (6.0)
Heart involvement	132/355 (37.2)
Pulmonary involvement	143 (29.6)
Liver involvement	128 (26.5)
Renal involvement	36 (7.5)
Autoimmune thyroiditis	46/401 (11.5)
Family history of rheumatic disease	46/442 (10.4)
Cytopenia	227/473 (48.0)
Anemia (Hb <110 g/L), n (%)	97/473 (20.5)
Leucopenia (<4×10^9 cells/L), n (%)	150/473 (31.7)
Thrombocytopenia (<100×10^9 cells/L), n (%)	32/473 (6.8)
Lymphopenia (<0.8×10^9 cells/L), n (%)	29/473 (6.1)
ANA positive, n (%)	431/479 (90.0)
RF positive, n (%)	253/389 (65.0)
Anti-Ro/SS-A positive, n (%)	363/471 (77.1)
Anti-La/SS-B positive, n (%)	225/471 (47.8)
High IgG levels (>17 g/L), n (%)	311/448 (69.4)
High IgA levels (>4 g/L), n (%)	162/448 (36.2)
High IgM levels (>2.3 g/L), n (%)	110/448 (24.6)
Low C3 levels (<0.9 g/L), n (%)	159/398 (39.9)
Low C4 levels (<0.1 g/L), n (%)	26/398 (7.3)

ANA = antinuclear antibodies, RF = rheumatoid factor, SS = Sjögren syndrome, WUSF = whole unstimulated salivary flow.

* See definitions of clinical features in the Methods section.

† Ocular dye positive is defined as ≥4 according to van Bijsterveld scoring system.

‡ Parotid sialography positive is defined as showing the presence of diffuse sialectasias (punctate, cavitary, or destructive pattern), without evidence of obstruction in major ducts.

§ Salivary scintigraphy is defined as showing delayed uptake, reduced concentration and/or delayed excretion of tracer.

acidosis (29/483, 6.0%), kidney stones and/or renal calcification (21/371, 5.7%), and renal insufficiency (26/483, 5.4%). In addition, there were 188 patients with abnormal liver tests, including abnormal liver function (107/483, 22.2%) and liver and spleen enlargement (71/483, 14.7%). Patients with systemic disease involvement had higher frequency of saprodontia, anti-Ro/SS-A, and anti-La/SS-B positivity and high levels of IgA and IgM, according to univariate analysis. Using multivariate analysis, we identified high levels of IgA ($P = 0.03$) and IgM ($P = 0.02$) as independent variables (Table 4).

Patients With Pulmonary Involvement

Among the 483 patients, 143 (29.6%) had pulmonary injury. These patients had a higher prevalence of parotid enlargement and purpura among the initial symptoms and greater ANA, anti-Ro/SS-A, and anti-La/SS-B positivity, and higher levels IgG, IgA, and IgM by univariate analysis. Multivariate analysis identified parotid enlargement ($P = 0.004$) and purpura ($P = 0.035$) among the initial symptoms and anti-La/SS-B ($P = 0.004$) positivity, and higher levels of IgG ($P = 0.049$) and IgA ($P = 0.026$) as independent variables (Table 5).

ANA-positive Patients

Compared with the ANA-negative patients, the ANA-positive patients had a higher frequency of systemic involvement (pulmonary involvement, heart involvement, and anemia) and altered immunological markers (RF, anti-Ro/SS-A, and anti-La/SS-B antibodies), according to univariate analysis. Multivariate analysis identified heart ($P = 0.040$) and anti-Ro/SS-A antibodies ($P = 0.001$) as independent variables (Table 6).

Patients with RF

Compared with the RF-negative patients, the RF-positive patients had a higher frequency of parotid enlargement, purpura, and flaccid paralysis because of hypokalemia, leucopenia, and positive immunological markers (ie, ANA, anti-Ro/SS-A and anti-La/SS-B antibodies, and higher IgG levels) by univariate analysis. Multivariate analysis identified leucopenia ($P = 0.021$), anti-La/SS-B ($P = 0.035$), and higher IgG levels ($P = 0.003$) as independent variables (Table 6).

Patients With Anti-Ro/La Antibodies

Compared with the Ro/La-negative patients, the Ro/La-positive patients had a higher frequency of glandular involvement (xerostomia, xerophthalmia, parotid enlargement, or saprodontia) and extraglandular symptoms (flaccid paralysis resulting from hypokalemia, arthritis, pulmonary involvement, liver involvement, or anemia), and positivity for immune markers (ANA and high IgG levels) by univariate analysis. Multivariate analysis identified saprodontia ($P = 0.01$), liver involvement ($P = 0.009$), ANA ($P < 0.001$), and high IgG ($P < 0.001$) levels as independent variables (Table 6).

Patients With Hypocomplementemia

Compared with the patients with normal C3 and C4 levels, the patients with hypocomplementemia had a lower mean age at diagnosis and a higher frequency of anemia in the univariate analysis. Multivariate analysis also identified the age at diagnosis ($P = 0.013$) and a higher frequency of anemia ($P < 0.001$) as independent variables (Table 6).

TABLE 2. Univariate and Multivariate Analyses of the Main Demographic, Clinical, and Immunologic Features in Patients with Primary SS, by to Sex

Variable	Male (n = 27)	Female (n = 456)	Univariate Analysis (2-tailed *P* Value)	Multivariate Analysis
Xerophthalmia, n (%)*	10 (37.0)	283 (60.7)	0.010	0.007
Arthritis†	11 (40.7)	75 (16.4)	0.003	0.006
Leucopenia ($<4 \times 10^9$ cells/L), n (%)*	4/21 (19.0)	166/449 (37.0)	0.033	—
ESR, M(P_{25}-P_{75}), months‡	20 (7∼36)	31 (16∼54)	0.0262	—
RF positive, n (%)*	8/23 (34.8)	238/366 (65.0)	0.004	—
Anti-La/SS-B positive, n (%)	7/26 (26.9)	218/445 (49.0)	0.029	—

ESR = erythrocyte sedimentation rate, RF = rheumatoid factor, SS = Sjögren syndrome.
* Chi-squared test.
† Fisher exact test.
‡ Rank-sum test.

Patients With High IgG Levels

Compared with the patients with normal IgG levels, the patients with high IgG levels had a higher frequency of purpura and positivity for immune markers (ANA, anti-Ro/SS-A, and anti-La/SS-B) by univariate analysis. Multivariate analysis identified ANA ($P = 0.01$) and RF ($P = 0.003$) as independent variables (Table 6).

DISCUSSION

SS is a chronic autoimmune disease that typically affects middle-aged women, and a genome-wide association study has shown that genetic factors may play an important role in its pathogenesis.[15] Although SS is classically considered to be an exocrine gland disease (mainly the salivary and lacrimal glands) that causes oral and ocular dryness, it is also characterized by diverse clinical manifestations. These manifestations can be related either to periepithelial infiltrates in parenchymal organs (kidney, lung, and liver) or to immune complex deposition because of B cell hyperactivity (purpura, peripheral neuropathy, or glomerulonephritis).[1,16,17] Some researchers have studied the factors that affect diagnosis,[12,13] and these analyses have yielded different results. In this study, we evaluated the clinical and immunological manifestations of primary SS in 483 consecutive Chinese patients, which allowed us to further confirm that xerostomia, xerophthalmia, ANA, anti-Ro/SS-A, RF, high IgG levels, and low C3 levels are the most frequently occurring features of SS. However, saprodontia manifestations were frequently observed in our study (54.0%), which are not included in the current classification criteria, and may be a strong suggestion for SS.

The expression of SS in males was characterized by a lower frequency of xerophthalmia, leucopenia, ESR, and RF or anti-La/SS-B positivity. These findings are consistent with a generally accepted idea in autoimmunity that women have higher levels of autoimmune processes (both clinical and serological) than men. Many previous studies have reported results[18–24] that also support this notion. The lower frequency of autoimmunity in men may make it more difficult to diagnose this disease early.

Age is regarded as an important factor at SS diagnosis.[2,13] Young-onset patients showed a low degree of sicca involvement and a high degree of immunological features in our study, indicating a specific pattern in the clinical expression of primary SS. The identification of this specific presentation pattern may allow earlier diagnoses in such patients, for whom the diagnosis may be complicated because of the less pronounced expression of sicca features. These findings confirm results in children and

TABLE 3. Univariate and Multivariate Analysis of the Main Demographic, Clinical, and Immunologic Features in Patients With Primary SS, According to Age at Diagnosis (35 Years' Old or Younger or Older Than 35 Years of Age)

Variable	Age at Diagnosis ≤35 years, N (%) (n = 75)	Age at Diagnosis >35 years, N (%) (n = 380)	Univariate Analysis (2-tailed *P* value)	Multivariate Analysis
Initial symptoms				
Sicca symptoms, n (%)*	46/72 (63.9)	289/373 (77.5)	0.014	—
Saprodontia, n (%)*	8/72 (11.1)	97/373 (26.0)	0.006	—
Purpura, n (%)†	12/73 (23.3)	24/349 (6.9)	0.004	—
Flaccid paralysis due to hypokalemia	8/72 (11.1)	17/373 (4.6)	0.027	—
Flaccid paralysis due to hypocytosis, n (%)†	16/72 (22.2)	33/373 (8.8)	0.001	0.044
Xerophthalmia, n (%)*	10 (37.0)	283 (60.7)	0.010	
Arthritis†	5 (6.7)	151 (39.7)	0.000	—
High IgG levels (>17 g/L), n (%)*	58 (77.3)	237 (62.4)	0.000	—
Low C3 levels (<0.9 g/L), n (%)*	41/71 (57.7)	111/306 (36.3)	0.001	0.006

SS = Sjögren syndrome.
* Chi-squared test.
† Fisher exact test.

TABLE 4. Univariate and Multivariate Analysis of the Main Demographic, Clinical, and Immunologic Features in Patients with Primary SS, According to the Presence or Absence of Systemic Involvement

Variable	Sicca-limited Disease, N (%) (n = 94)	Systemic Involvement, N (%) (n = 384)	Univariate Analysis (2-tailed *P* Value)	Multivariate Analysis
Saprodontia, n (%)	41 (43.6)	220 (57.3)	0.024	—
Anti-Ro/SS-A positive, n (%)	61/91 (67.0)	302/380 (79.5)	0.011	—
Anti-La/SS-B positive, n (%)	32/91 (35.2)	193/380 (50.8)	0.007	—
High IgA levels (>4 g/L), n (%)	20/89 (22.5)	142/360 (39.4)	0.003	0.030
High IgM levels (>2.3 g/L), n (%)	11/89 (12.4)	99/261 (37.9)	0.003	0.020

SS = Sjögren syndrome. Chi-squared test.

adolescents,[25] and in other young-onset SS populations.[12,14] Some studies have shown that the clinical presentation of elderly patients was diametrically opposite to young-onset SS patients, with a lower prevalence of some systemic and immunological features, which may reflect senescence of the immune system.[13,26] However, our data did not support this pattern, although we caution that our sample of elderly patients was very small (n = 18).

The subset of patients with systemic disease involvement showed an increased prevalence of saprodontia, anti-Ro/SS-A, and anti-La/SS-B positivity, and higher levels of IgG and IgM, which may reflect an excessive immune process. The prevalence of saprodontia was highest among all physical signs (54.0%) on registry. The occurrence of saprodontia, resulting from reduced saliva production as a consequence of immune-mediated injury of the salivary glands, is a prominent sign in SS patients. Thus, typical saprodontia should be included in the diagnostic criteria, although it may be less common at the early disease stage.

Patients with pulmonary involvement had a greater prevalence of parotid enlargement and purpura among the initial symptoms, and a greater prevalence of anti-La/SS-B antibodies, as well as higher IgG and IgA levels by multivariate analysis, rather than differences in anti-Ro/SS-A antibodies. This finding was inconsistent with other studies,[27–29] but a previous study reported that anti-La/SS-B levels had a higher specificity than anti-Ro/SS-A levels (92.6% vs 85.7%).[29] Therefore, using anti-La/SS-B to predict pulmonary involvement in SS patients should be a cause for concern.

Positivity for autoantibodies is important in diagnosing SS and represents 1 of the 6 AECG criteria for SS. The 1993 European Criteria[30] include the presence of $\geq$1 of 4 antibodies (ANA, RF, Ro/SS-A, and/or La/SS-B), whereas the 2002 Criteria includes only anti-Ro/SS-A and/or anti-La/SS-B antibodies.[14] ANA is the most frequently detected antibody in primary SS (90% in the study presented here) and is closely associated with various extraglandular and immunological features; RF is also associated with the main extraglandular, histopathological, hematological, and immunological features of SS.[19,26,31] Thus, a patient with sicca syndrome, positive ocular tests and parotid scintigraphy, and positive ANA and/or RF should be diagnosed with SS, even if the anti-Ro/La antibodies are negative. ANA and RF determinations may play a central role in differentiating SS from non-autoimmune causes of sicca syndrome, although they are not included in the AECG criteria. Considering the findings of our study and others[13] we suggest an important diagnostic role for ANA/RF testing, as did the American College Of Rheumatology (ACR)[32] in 2012.

Anti-Ro/SSA and anti-La/SSB antibodies can be detected in approximately 50% to 70% of primary SS patients[33] and associated with some presentations. In the study presented herein, the subset of patients with anti-Ro/La antibodies not only had a higher prevalence of sicca symptoms but also showed extraglandular involvement, confirming previous reports that

TABLE 5. Univariate and Multivariate Analysis of the Main Demographic, Clinical, and Immunological Features in Patients with Primary SS, According to Pulmonary Involvement (Years or N [%])

Variable	Pulmonary Involvement No. (%)		Univariate Analysis (2-tailed *P* value)	Multivariate Analysis
	Yes (n = 143)	No (n = 340)		
Initial symptoms				
Parotid enlargement, n (%)*	30/140 (21.4)	34/332 (10.2)	0.001	0.004
Purpura, n (%)*	17/140 (12.1)	19/332 (5.7)	0.016	0.035
ANA positive, n (%)†	136/141 (96.5)	295/338 (87.3)	0.002	0.143
Anti-Ro/SS-A positive, n (%)†	118/141 (83.7)	245/330 (74.2)	0.026	0.281
Anti-La/SS-B positive, n (%)†	87/141 (61.7)	138/330 (41.8)	0.000	0.004
High IgG levels (>17 g/L), n (%)†	109/135 (80.7)	203/314 (64.6)	0.001	0.049
High IgA levels (>4 g/L), n (%)†	66/135 (48.9)	96/314 (30.6)	0.000	0.026
High IgM levels (>2.3 g/L), n (%)†	44/135 (32.6)	66/314 (21.0)	0.009	0.258

ANA = antinuclear antibodies, SS = Sjögren syndrome.
* Fisher's exact test.
† Chi-squared test.

TABLE 6. Analysis of the Main Demographic, Clinical, and Immunological Features in Patients with Primary SS, According to Presence or Absence of the Main Immunological Markers

Variable	ANA (+), N (%) (n = 431)	RF (+), N (%) (N = 253)	SSA (+), N (%) (N = 363)	Low c3/c4, No. (%) (N = 161)	High IgG, N (%) (n = 311)
Sex, female, n (%)	409 (94.9)	238 (94.1)	342 (94.2)	153 (95.0)	298 (95.8)
Age at onset, mean (SD), years	41.6 (11.2)	41.1 (11.2)	41.3 (10.9)	40.5 (12.4)	40.9 (11.0)
Age at diagnosis, mean (SD), y	55.1 (10.8)	55.0 (10.9)	54.8 (10.4)	53.0 (12.3)*	54.8 (10.9)
Xerostomia, n (%)	330/431 (76.6)	202/273 (74.0)	288/363 (79.3)**	52/161 (32.3)	242 (77.8)
Xerophthalmia, n (%)	259/431 (60.1)	156/253 (61.7)	232/363 (63.9)**	94/161 (58.4)	191 (61.4)
Parotid enlargement, n (%)	90/431 (20.9)	65/253 (25.7)**	85/363 (23.4)**	33/161 (20.5)	67 (21.5)
Saprodontia, n (%)	238/431 (55.2)	140/273 (51.3)	211/363 (58.1)**	87/161 (54.0)	176 (56.6)
Purpura, n (%)	43/431 (10.0)	30/253 (11.9)**	39/363(10.7)	16/161 (9.9)	36 (11.6)**
Flaccid paralysis due to hypokalemia	26/431 (6.0)	21/253 (8.3)**	26/363 (7.2)**	9/161 (5.6)	20 (6.4)
Arthritis	74/431 (17.2)	43/253 (17.0)	71/363 (19.6)**	29/161 (18.0)	58 (18.6)
Pulmonary involvement	136/431 (31.6)**	85/253(33.6)	118/363 (32.5)**	48/161 (29.8)	202 (65.0)
Liver involvement	109/431 (25.3)	63/253 (24.9)	106/363 (29.2)**	41/161 (25.5)	80 (25.7)
Heart involvement	127/321 (39.6)**	74/191 (38.7)	104/273 (38.1)	51/132 (38.6)	90/239 (37.7)
Anemia (Hb <110 g/L), n (%)	93/423 (22.0)**	60/247 (24.3)	82/356 (23.0)**	48/158 (30.4)**	67/306 (21.9)
Leucopenia (<4×10^9 cells/L), n (%)	140/424 (33.0)	90/237 (38.0)**	117/357 (32.8)	64/158 (40.5)	106/306 (34.6)
ANA positive, n (%)	NA	243/253 (96.0)**	348/363 (95.9)**	150/161 (93.2)	298 (95.8)**
RF positive, n (%)	243/409 (59.4)**	NA	253/341 (74.2)	93/114 (81.6)	198/272 (72.8)**
Anti-Ro/SS-A positive, n (%)	348/431 (85.1)**	253/253 (100.0)**	NA	126/158 (79.7)	266 (85.5)**
Anti-La/SS-B positive, n (%)	219/431 (50.8)**	142/253 (56.1)**	NA	78/158 (49.4)	166/309 (53.7)**
High IgG levels (>17 g/L), n (%)	298/407 (73.2)	198/244 (81.1)**	266/345 (77.1)**	109/157 (69.4)	NA

ANA = antinuclear antibodies, RF = rheumatoid factor, SD = standard deviation, SS = Sjögren syndrome.
* $P < 0.05$, lower compared with the opposite group.
** $P < 0.05$, higher compared with the opposite group.

showed a close correlation between positivity for these autoantibodies and extraglandular manifestations,[34–38] serological markers,[38,39] and a higher focus score in salivary gland biopsies.[31,40] These findings confirm that anti-Ro/La antibodies are considered to be a mandatory criterion for primary SS. However, the inclusion of positivity for anti-Ro/La antibodies as a mandatory criterion may limit the diagnosis of some cases of primary SS because some subsets, such as males and those with

TABLE 7. Main Epidemiologic, Clinical and Immunological Features in a Large Series of Patients with Primary SS

Feature	Present Report*	Ramos-Casals et al[13]	Ioannidis et al[44]	Alamanos et al[45]	Theander et al[42]	Garcia-C et al[46]
No. of patients	483	1010	723	422	265	400
Country	China	Spain	Greece	Greece	Sweden	Spain
Sex (female) (%)	94.4	93	94	95	91	93
Female:male ratio	17:1	13:1	16:1	20:1	10:1	14:1
Mean age at diagnosis, y	49	53	—	55	56	53
Xerostomia (%)	77.2	96	95	94	—	98
Xerophthalmia (%)	60.5	96	96	100	—	93
Parotid enlargement (%)	20.32	27	44	26	26	18
Articular involvement (%)	38.1	48	—	39	—	37
Raynaud phenomenon (%)	—	18	—	35	—	16
Pulmonary involvement (%)	29.6	11	—	3	—	9
Peripheral neuropathy (%)	—	11	—	—	—	7
Vasculitis (%)	—	9	8	5	—	12
Renal involvement (%)	7.5	5	—	—	—	6
CNS involvement (%)	—	2	—	—	—	1
ANA (%)	90.0	85	80	94	—	74
Anti-Ro/SS-A (%)	77.1	52	48	50	56	40
RF (%)	65.0	48	52	32	51	38
Anti-La/SS-B (%)	47.8	34	27	40	—	26
Low C3 %	39.9	9	3	—	—	3
Low C4 (%)	7.3	9	20	—	—	8
Cryoglobulins (%)	—	10	—	28	—	9

ANA = antinuclear antibodies, CNS = central nervous system, SS = Sjögren syndrome.
* Not all percentages are based on 483 patients; denominators differ because of varying number of patients for each feature. See Table 1 for details.

sicca-limited disease, had a lower prevalence of anti-Ro/La antibodies, thereby reducing their probability of fulfilling the 2002 criteria. The newly proposed ACR classification criteria for SS, in which anti-Ro/La antibodies are not mandatory, solved this problem.[32]

High IgG levels are a common feature of SS and might reflect greater B cell activation.[41] In our study, patients with high IgG levels had a higher prevalence of purpura and immunological markers (ANA, RF, anti-Ro/SS-A, and anti-La/SS-B) that indicate hyperactive disease. Hypocomplementemia had been confirmed to be related to a lower mean age and a higher frequency of vasculitis, RF, and B cell lymphoma.[13] We found a close association between hypocomplementemia and a lower mean age at diagnosis and a higher frequency of anemia. Ioannidis et al[17] may have been the first to suggest a prognostic role for low C4 levels, which was confirmed, together with low C3 levels, by Theander et al.[42] Some studies have also suggested a negative association between hypocomplementemia and survival.[21,42,43] These data, all obtained from large prospective series of patients, confirmed that complement measurements should be considered as key immunological markers in the follow-up of patients with primary SS (as complement and anti-DNA levels are indicative of systemic lupus erythematosus).

We found some marked differences in the main features of the current cohort of patients compared with those reported in previous studies[13,42–46] (Table 7), including a lower prevalence of xerostomia and xerophthalmia, a higher prevalence of pulmonary involvement, a higher frequency of the main autoantibodies (ANA, RF, anti-Ro/La), and the prevalence of low C3 levels. These differences might be affected by patient ethnicity or clinical treatments. The lower frequencies of xerostomia and xerophthalmia in the present cohort compared with other cohorts could also be due to cultural differences and education levels. Indeed, the majority of Chinese people believe that dry mouth and dry eye are not significant problems, which were reflected in another study carried out in China.[47] Pulmonary involvement in the present study was higher than in other studies; therefore, it should be included in routine screenings for SS patients in China.

Conclusively, some new associations were found in the present study. First, we found a high prevalence of saprodontia in Chinese SS patients and maybe a strong suggestion for SS. Second, we found a high prevalence of low C3 levels in Chinese SS patients and should be an important follow-up item. Third, we found that the prevalence of anti-La/SS-B was high in patients with pulmonary involvement, which may predict pulmonary involvement for Chinese SS patients. The broad heterogeneity in the clinical findings of patients with primary SS that we observed in this study shows that our understanding of this systemic autoimmune disease is still evolving and that the different criteria used to diagnose primary SS can lead to different appraisals of the disease. This study had some limitations. Although the study was multicentric, we were unable to accurately represent the entire spectrum of Chinese SS patients. Furthermore, as this was a cross-sectional study, we could not address dynamic changes in the patients' condition; therefore, we plan on summarizing the clinical information for these patients in a period manner.

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