Distinct clinical phenotypes of primary Sjögren's syndrome differ by onset age: a retrospective study of 742 cases and literature review

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Abstract

Objective

To study the clinical characteristics of primary Sjögren's syndrome (pSS) with different onset age, and perform a review of the literature to confirm if the clinical phenotypes are affected by onset age in patients with pSS.

Methods

Data of 742 patients with pSS were retrospectively analysed. Patients were divided into three groups according to onset age: young-onset pSS (YopSS, <35 years), adult-onset pSS (AopSS, ≥35 and ≤65 years), and elderly-onset pSS (EopSS, >65 years). Clinical characteristics were compared among three groups and further multiple comparisons were conducted by Bonferroni adjustment. The Chi-squared test for linear-by-linear association was used to explore variation tendency.

Results

This study included 105 (14.2%), 533 (71.8%), and 104 (14.0%) cases of YopSS, AopSS, and EopSS, respectively. YopSS demonstrated lower prevalence of dry mouth, abnormal Schirmer I tests, and interstitial lung disease (ILD), but higher proportions of low C3 and C4 levels, and ANA, anti-SSA, anti-SSB, and rheumatoid factor (RF) positivity than AopSS and EopSS. The proportions of dry mouth ($p=0.004$), abnormal Schirmer I tests ($p=0.002$), and ILD ($p<0.001$) tended to increase with the increase of onset age, while the prevalence of leukopenia ($p=0.011$), low C3 ($p=0.001$), low C4 ($p=0.001$), and ANA ($p<0.001$), anti-SSA ($p<0.001$), anti-SSB ($p<0.001$) and RF ($p<0.001$) positivity tended to decrease with an increase in onset age.

Conclusion

YopSS demonstrated less dryness and ILD, but more immunologic disorders. ILD prevalence were directly proportional to onset age of pSS; however, leukopenia, hypocomplementaemia, and autoantibody positivity showed opposite trends.

Key words

Sjögren's syndrome, onset age, clinical phenotypes, interstitial lung disease

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Introduction

Primary Sjögren's syndrome (pSS) is a chronic systemic autoimmune disease characterised by B-cell hyperactivity and lymphocytic infiltration of exocrine glands, that presents as sicca syndrome (1). It affects 0.3-1 per 1000 of the general population with a peak incidence at approximately 50 years of age (2). The clinical phenotype of pSS varies from a benign glandular disorder to aggressive systemic involvement, and approximately 30% to 40% of patients have systemic manifestations such as interstitial lung disease (ILD) (3). Additionally, pSS is associated with the development of a lymphoproliferative disorder in 5% of patients that contributes greatly to the mortality of the disease (4). It is known that the extent and severity of pSS depend on many parameters including the genetic background, environmental factors, and some demographic characteristics such as age. Although pSS can occur in patients of all ages, it primarily affects women between the fourth and sixth decades of life (5). As the functional status of the human immune system changes with age, it is reasonable to expect that age may interfere with the clinical phenotypes of pSS. Previous studies have shown that the onset often precedes the diagnosis by 5 years or more in pSS (6, 7). Therefore, differences in clinical phenotypes across distinct onset age groups may reflect underlying pathogenetic mechanisms of pSS.

To date, some studies have attempted to explore the clinical characteristics of pSS patients with different onset age (5-17). Nevertheless, almost half of the studies focused on age at diagnosis of pSS (5, 8-12), rather than onset age as the time of pSS occurrence. Because the onset of pSS and especially the occurrence of sicca symptoms often precedes the time of pSS diagnosis, it seems that the time of disease occurrence may better represent the underlying pathogenetic process of pSS. What's more, regardless of the definition of onset age, the conclusions of previous studies are controversial. Focusing on previous studies, it is anticipated that almost 30% of pSS patients have an early or late onset age, depending on the cut-offs of age group (35-40 or 65-70 years, respectively) (6, 7, 13-17). Most studies had limited sample size and only explored the clinical characteristics of either early or late onset pSS (14-17). Only two studies focused on differences among pSS patients with early, typical, and late onset age, but got contrary results (7, 13). Information on clinical phenotypes among the three different onset pSS in Asia, and specifically China, is rather limited. Moreover, no study investigates the variation tendency of important phenotypes, such as ILD, along the onset age of pSS. We therefore conducted this retrospective study and review of the literature to further investigate the clinical phenotypes of pSS with the three different onset age in Chinese patients to inform clinical practice.

Materials and methods

Study population

In this study, the data from 742 consecutive patients with pSS who were treated at the China-Japan Friendship Hospital between January 2013 and December 2020 were retrospectively analysed (Fig. 1). The diagnosis of pSS was based on the 2002 American-European Consensus Group (AECG) criteria (18) or the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria (19). Patients with cancer, pregnancy or secondary SS were excluded. Records missing important data, such as onset age or diagnostic indicators, were also excluded.

The onset of pSS was defined as the first appearance of disease-related manifestations, such as sicca symptoms, parotid enlargement, arthralgia, or purpura. Disease duration was calculated by the time span between pSS onset and diagnosis. In accordance with the cut-offs of onset age group in most previous studies, we divided patients into three groups according to onset age of pSS, as follows: young-onset pSS (YopSS, <35 years), adult-onset pSS (AopSS, ≥35 and ≤65 years), and elderly-onset pSS (EopSS, >65 years). This study

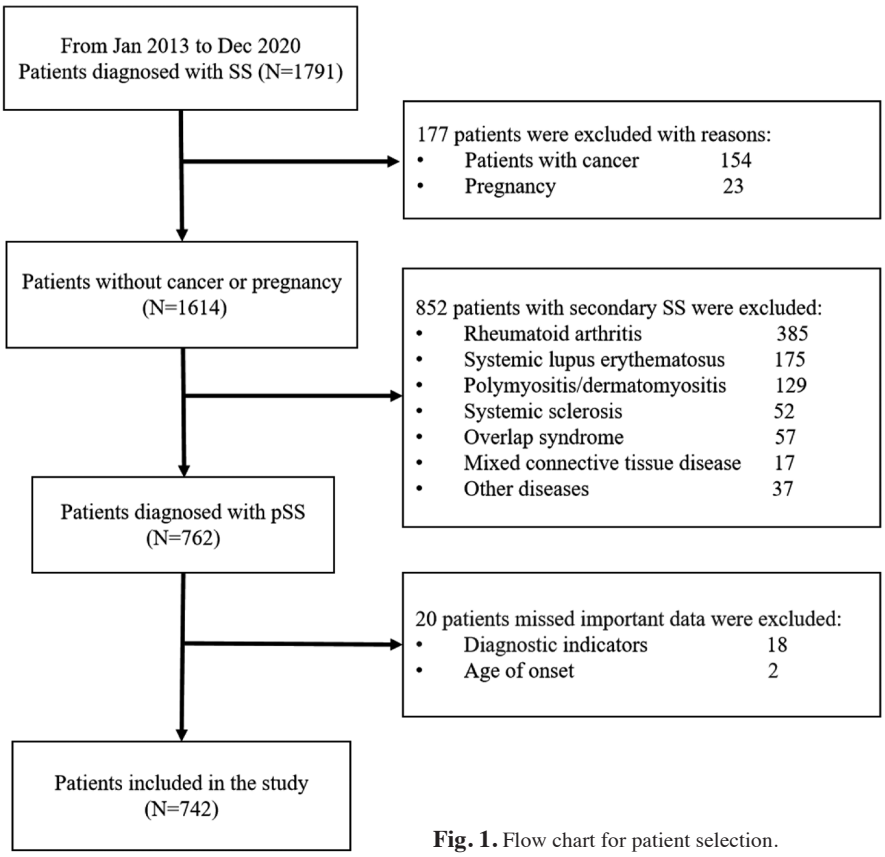

Fig. 1. Flow chart for patient selection.

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 datasets were anonymised.

Data collection

Clinical data including patient demographics, clinical manifestations, laboratory findings, minor salivary gland (MSG) biopsy findings, and diagnosis were collected from medical records of eligible patients and the hospital information system. For each patient, all clinical data were collected at the time of disease diagnosis. Clinical manifestations included symptoms related to pSS such as dryness, arthralgia, and ILD. An abnormal Schirmer I test was defined by a result of ≤5 mm/5 min. Arthralgia was defined as joint pain with morning stiffness or synovitis. ILD is a group of respiratory diseases affecting the interstitium of the lung. It was detected by high-resolution computed tomography (HRCT), evaluated by two experienced radiologists, and diagnosed by clinical doctors. The main morphology observed in ILD on HRCT include variable combination of reticular abnormalities, ground-glass opacities, nodules, consolidation, cysts, honeycombing and bronchiectasis (20). Laboratory indicators included a full blood test; levels of immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM), complement 3 (C3), and complement 4 (C4); erythrocyte sedimentation rate (ESR); and titres of antinuclear antibodies (ANA), anti-SSA antibody, anti-Ro52 antibody, anti-SSB antibody, anti-centromere protein B (CENPB) antibody, anti-ribonucleoprotein (RNP) antibody, and rheumatoid factor (RF).

All tests were performed using commercial techniques standardized at the China-Japan Friendship Hospital. Leukopenia was defined by white blood cell counts of <4.00 x 10^9/L, neutropenia was defined by neutrophil counts of <1.5 × 10^9/L, lymphopenia was defined by lymphocyte counts of <0.8×10^9/L, anaemia was defined by haemoglobin concentrations of <110 g/L, and thrombocytopenia was defined by platelet counts of <100 × 10^9/L. Hyper-IgA, hyper-IgG, and hyper-IgM were defined by individual immunoglobin levels of >3.78 g/L, >16.2 g/L, and >2.63 g/L, respectively. Low C3 and low C4 were defined at levels of <0.7 g/L and <0.16 g/L, respectively. Elevated ESR was defined by values exceeding 20 mm/h. The ANA titre was determined by indirect immunofluorescence assay in HEp2 cells, and positivity was defined by a titre of ≥1:160. Anti-SSA and other autoantibodies were tested using commercial immunoblotting kits. RF was determined by immunoturbidimetric assay, and a level of >20 IU/mL was considered positive. The MSG biopsies were performed by professional stomatologists and the pathological diagnoses were determined by pathologists at the China-Japan Friendship Hospital; positive biopsy was defined by focal lymphocytic sialadenitis with a focus score of ≥1. A focus score was defined as more than 50 lymphocytes per 4 mm^2 of glandular tissue with normal surrounding acinar tissue (18).

Statistical analysis

SPSS (Version 20.0) software was used for data analyses. Categorical data have been summarized by frequencies and percentages. Continuous data have been presented as medians with interquartile ranges (IQRs) for non-normal distributions. The Shapiro-Wilk test was conducted to detect normality. For three-group comparisons, the Kruskal-Wallis H test was used for non-normally distributed continuous data; the Chi-squared and Fisher's exact tests were used to compare binary data, as appropriate. Multiple comparisons were further conducted using the post-hoc analysis corrected by Bonferroni adjustment. The Chi-squared test for linear-by-linear association (LLA) was used to explore variation tendency among the three groups. GraphPad Prism 9.0.0 was used to create trend charts. A two-sided *p*-value of <0.05 was considered significant.

Results

Demographic characteristics of included patients

A total of 742 patients with pSS were included in this study, among whom

Table I. Comparison of clinical characteristics among patients with different onset age of pSS.

Clinical characteristics	Total (n=742)	Young onset (n=105)	Adult onset (n=533)	Elderly onset (n=104)	*p*-value
Gender (female)	649 (87.5)	97 (92.4)	471 (88.4) [b]	81 (77.9) [c]	**0.003**
Age at onset (years)	52.0 (41.0-61.0)	28.0 (24.0-32.0) [a]	52.0 (45.0-59.0) [b]	69.0 (68.0-72.75) [c]	**<0.001**
Age at diagnosis (years)	58.0 (49.0-66.0)	34.0 (29.5-45.0) [a]	57.0 (50.0-64.0) [b]	72.0 (70.0-74.0) [c]	**<0.001**
Disease duration (months)	36.0 (11.75-96.0)	72.0 (24.0-162.0) [a]	48.0 (12.0-96.0) [b]	12.0 (3.25-36.0) [c]	**<0.001**
Clinical manifestations					
Dry mouth	647 (87.2)	82 (78.1) [a]	470 (88.2)	95 (91.3) [c]	**0.007**
Dry eye	593 (79.9)	75 (71.4)	436 (81.8)	82 (78.8)	0.051
Fatigue	358 (48.2)	39 (37.1) [a]	273 (51.2)	46 (44.2)	**0.021**
Arthralgia	298/733 (40.7)	41/103 (39.8)	227/526 (43.2) [b]	30 (28.8)	**0.025**
Schirmer I test ≤5 mm/5 min	677 (91.2)	86 (81.9) [a]	493 (92.5)	98 (94.2) [c]	**0.001**
Dental caries	296 (39.9)	46 (43.8)	225 (42.2) [b]	25 (24.0) [c]	**0.002**
Parotid enlargement	117/741 (15.8)	23 (21.9)	80 (15.0)	14/103 (13.6)	0.168
Interstitial lung disease	257 (34.6)	15 (14.3) [a]	192 (36.0)	50 (48.1) [c]	**<0.001**

All values are presented as n (%) or median (interquartile range). Young-onset < 35 years; adult-onset: ≥35 and ≤65 years; elderly-onset >65 years.
[a] $p_{adjusted}$ <0.05 (young-onset pSS *vs*. adult-onset pSS) on the basis of *post-hoc* analysis corrected by Bonferroni adjustment.
[b] $p_{adjusted}$ <0.05 (adult-onset pSS *vs*. elderly-onset pSS) on the basis of *post-hoc* analysis corrected by Bonferroni adjustment.
[c] $p_{adjusted}$ <0.05 (young-onset pSS *vs*. elderly-onset pSS) on the basis of *post-hoc* analysis corrected by Bonferroni adjustment.

649 (87.5%) were women. Among the 742 included patients, all (100.0%) fulfilled the 2002 AECG criteria of pSS, 4 (0.5%) dissatisfied the 2016 ACR/EULAR classification criteria, and 738 (99.5%) met both criteria. The median age at onset of pSS was 52 (IQR 41.0-61.0) years, the median age at diagnosis of pSS was 58 (IQR 49.0-66.0) years, and the median duration of pSS was 36 (IQR 12.0-96.0) months. Among the 742 patients with pSS, 105 (14.2%) had YopSS, 533 (71.8%) had AopSS, and the remaining 104 (14.0%) had EopSS.

Significant differences were found among the three onset age groups in terms of proportions of gender (p=0.003) and disease duration (p<0.001). After Bonferroni adjustment, multiple comparisons showed that the EopSS group had a lower proportion of females (77.9% vs. 88.4% and 92.4%, respectively, $p_{adjusted}$ <0.05) and shorter disease duration (12.0 [3.5-36.0] vs. 48.0 [12.0-96.0] and 72.0 [24.0-162.0], respectively, $p_{adjusted}$ <0.05) than the AopSS and YopSS groups (Table I).

Clinical manifestations in pSS patients with different onset age

As shown in Table I, patients with pSS commonly had dry mouth (87.2%) and dry eyes (79.9%). On ocular evaluation, the majority (91.2%) of patients demonstrated abnormal Schirmer I test results. Some patients had fatigue (48.2%), arthralgia (40.7%), dental caries (39.9%), and parotid enlargement (15.8%). ILD was found in 34.6% patients with pSS. Significant differences were detected in the proportions of dry mouth (p=0.007), fatigue (p=0.021), arthralgia (p=0.025), abnormal Schirmer I tests (p=0.001), dental caries (p=0.002), and ILD (p<0.001) among the three onset age groups. No difference was detected in terms of dry eyes and parotid enlargement.

Multiple comparisons showed that patients with YopSS demonstrated lower proportions of dry mouth (78.1% *vs*. 88.2% and 91.3%, respectively, $p_{adjusted}$ <0.05), abnormal Schirmer I tests (81.9% *vs*. 92.5% and 94.2%, respectively, $p_{adjusted}$ <0.05), and ILD (14.3% vs. 36.0% and 48.1%, respectively, $p_{adjusted}$ <0.05) than those with AopSS and EopSS. Patients with EopSS had a lower percentage of dental caries (24.0% vs. 42.2% and 43.8%, respectively, $p_{adjusted}$ <0.05) than those with AopSS and YopSS. Moreover, the LLA test showed that the proportions of dry mouth (p_{trend} =0.004), abnormal Schirmer I tests (p_{trend} =0.002), and ILD (p_{trend} <0.001) tended to increase with the increase of onset age, and the prevalence of dental caries showed opposite trends (p_{trend} =0.004) (Fig. 2A). In addition, the AopSS group showed a higher proportion of fatigue (51.2% vs 37.1%, $p_{adjusted}$ <0.05) than the YopSS group and more arthralgia (43.2% *vs*. 28.8%, $p_{adjusted}$ <0.05) than the EopSS group (Table I). However, no difference was detected in terms of fatigue and arthralgia in the LLA test.

Laboratory characteristics of patients with different onset age

As shown in Table II, ANA titres of ≥1:160 were found in 64.2% of included patients with pSS. Anti-SSA, anti-Ro52, anti-SSB, anti-CENPB, anti-RNP, and RF positivity were observed in 67.4%, 56.1%, 28.4%, 8.2%, 8.1%, and 44.5% of included patients, respectively. Among the 418 patients who underwent MSG biopsies, 97.8% showed positive findings. Among the three onset age groups, significant differences were identified in the proportion of leukopenia (p=0.037), anaemia (p=0.003), hyper-IgG (p=0.049), low C3 (p=0.003), low C4 (p=0.001), elevated ESR (p=0.036), and ANA (p=0.001), anti-SSA (p<0.001), anti-Ro52 (p=0.017), anti-SSB (p<0.001), anti-CENPB (p=0.034), and RF (p<0.001) positivity. However, no significant difference was found among the three onset age groups in terms of the percentage of neutropenia, lymphopenia, thrombocytopenia, hyper-IgA, hyper-IgM, and anti-RNP and MSG biopsy positivity.

Multiple comparisons showed that patients with YopSS demonstrated higher percentages of leukopenia (33.0% *vs*. 17.5%, $p_{adjusted}$ <0.05), and anti-Ro52 (67.7% *vs*. 48.1%, $p_{adjusted}$ <0.05) and anti-CENPB (11.5% *vs*. 2.0%, $p_{adjusted}$

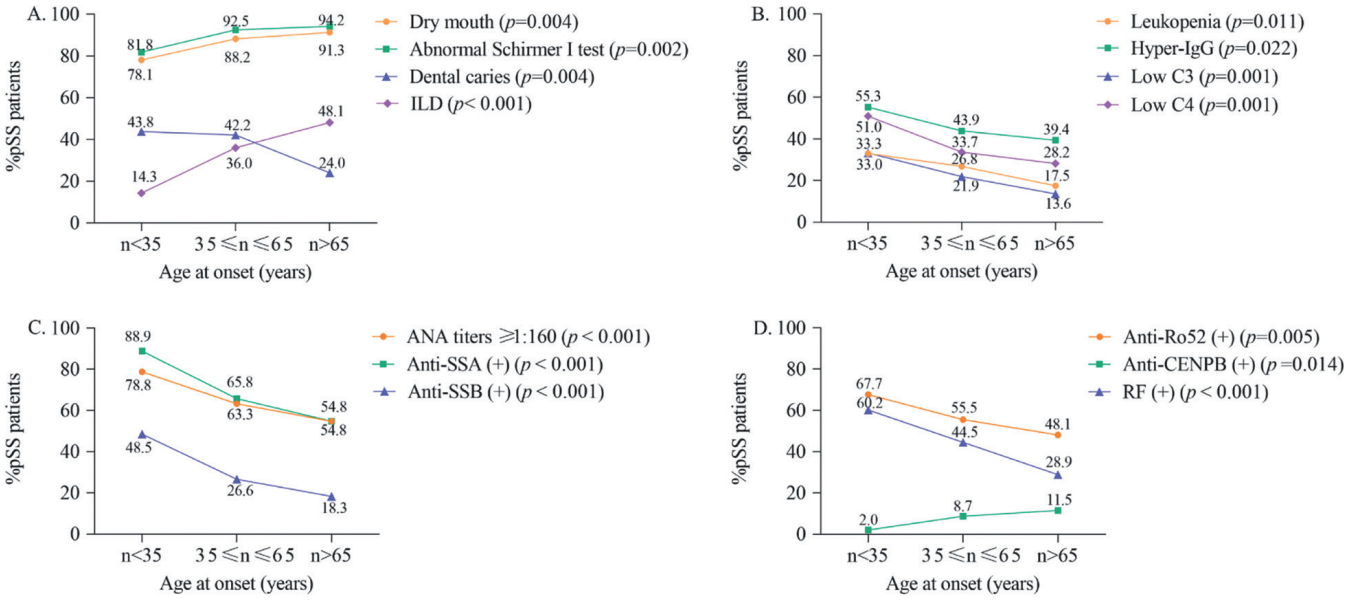

Fig. 2. Trends in the prevalence of clinical phenotypes based on age at onset.
ILD: interstitial lung disease; IgG: immunoglobulin G; C3: complement 3, C4: complement 4; ANA: antinuclear antibodies; anti-CENPB: anti-centromere protein B; RF: rheumatoid factor.

Table II. Comparison of laboratory characteristics among patients with different onset age of pSS.

Laboratory findings	Total (n=742)	Young onset (n=105)	Adult onset (n=533)	Elderly onset (n=104)	*p*-value
Leukopenia (<4.0×10⁹/L)	193/732 (26.4)	34/103 (33.0)	141/526 (26.8)	18/103 (17.5) [c]	**0.037**
Neutropenia (<1.5×10⁹/L)	54/732 (7.4)	9/103 (8.7)	42/526 (8.0)	3/103 (2.9)	0.168
Lymphopenia (<0.8×10⁹/L)	51/732 (7.0)	12/103 (11.7)	35/526 (6.7)	4/103 (3.9)	0.079
Anaemia (Hb <110 g/L)	135/732 (18.4)	30/103 (29.1) [a]	82/526 (15.6)	23/103 (22.3)	**0.003**
Thrombocytopenia (<100×10⁹/L)	93/732 (12.7)	18/103 (17.5)	61/526 (11.6)	14/103 (13.6)	0.250
Hyper-IgA (>3.78 g/L)	189/729 (25.9)	29/103 (28.2)	126/522 (24.1)	34 (32.7)	0.164
Hyper-IgG (>16.2 g/L)	327/729 (44.9)	57/103 (55.3)	229/522 (43.9)	41 (39.4)	**0.049**
Hyper-IgM (>2.63 g/L)	63/729 (8.6)	6/103 (5.8)	49/522 (9.4)	8 (7.7)	0.467
Low C3 (<0.70 g/L)	162/725 (22.3)	34/102 (33.3) [a]	114/520 (21.9)	14/103 (13.6) [c]	**0.003**
Low C4 (<0.16 g/L)	256/725 (35.3)	52/102 (51.0) [a]	175/520 (33.7)	29/103 (28.2) [c]	**0.001**
Elevated ESR (>20 mm/h)	349/696 (50.1)	58/99 (58.6)	236/501 (47.1)	55/96 (57.3)	**0.036**
ANA titres ≥1:160	461/718 (64.2)	78/99 (78.8) [a]	326/515 (63.3)	57 (54.8) [c]	**0.001**
Positive anti-SSA	484/718 (67.4)	88/99 (88.9) [a]	339/515 (65.8)	57 (54.8) [c]	**<0.001**
Positive anti-Ro52	403/718 (56.1)	67/99 (67.7)	286/515 (55.5)	50 (48.1) [c]	**0.017**
Positive anti-SSB	204/718 (28.4)	48/99 (48.5) [a]	137/515 (26.6)	19 (18.3) [c]	**<0.001**
Positive anti-CENPB	59/718 (8.2)	2/99 (2.0)	45/515 (8.7)	12 (11.5) [c]	**0.034**
Positive anti-RNP	58/718 (8.1)	12/99 (12.1)	41/515 (8.0)	5 (4.8)	0.158
Positive RF [d]	309/694 (44.5)	59/98 (60.2) [a]	222/499 (44.5) [b]	28/97 (28.9) [c]	**<0.001**
Positive MSG biopsy [e]	409/418 (97.8)	47/49 (95.9)	305/309 (98.7)	57/60 (95.0)	0.119

All values are presented as n (%) or median (interquartile range). Young-onset < 35 years; adult-onset: ≥35 and ≤65 years; elderly-onset >65 years.
Hb: haemoglobin. IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; C3: complement 3, C4: complement 4; ESR: erythrocyte sedimentation rate; ANA: antinuclear antibodies; anti-CENPB: anti-centromere protein B; anti-RNP: anti-ribonucleoprotein; RF: rheumatoid factor; MSG: minor salivary gland.
[a] $p_{adjusted}$ <0.05 (young-onset pSS *vs*. adult-onset pSS) on the basis of *post-hoc* analysis corrected by Bonferroni adjustment.
[b] $p_{adjusted}$ <0.05 (adult-onset pSS *vs*. elderly-onset pSS) on the basis of *post-hoc* analysis corrected by Bonferroni adjustment.
[c] $p_{adjusted}$ <0.05 (young-onset pSS *vs*. elderly-onset pSS) on the basis of *post-hoc* analysis corrected by Bonferroni adjustment.
[d] positive RF>20 IU/mL.

<0.05) positivity than those with EopSS and a higher prevalence of anaemia (29.1% vs 15.6%, $p_{adjusted}$ <0.05) than those with AopSS. In addition, patients with YopSS demonstrated higher proportions of low C3 (33.3% *vs*. 21.9% and 13.6%, respectively, *p*<0.05), low C4 (51.0% *vs*. 33.7% and 28.2%, respectively, *p*<0.05), and ANA (78.8% *vs*. 63.3% and 54.8%, respectively, *p*<0.05), anti-SSA (88.9% *vs*. 65.8% and 54.8%, respectively, *p*<0.05), anti-SSB (48.5% *vs*. 26.6% and 18.3%, respectively, *p*<0.05), and RF (60.2% *vs*. 44.5% and 28.9%, respectively, *p*<0.05) positivity than those with AopSS and EopSS. On Bonferroni adjustment, no between-group differences were found in terms of elevated ESR and hyper-IgG.

The LLA test showed that the proportions of leukopenia (p_{trend} =0.011), low C3 (p_{trend} =0.001), low C4 (p_{trend} =0.001), and ANA (p_{trend} <0.001), an-

Table III. Clinical characteristics of pSS with different onset age: review of the literature.

Study ID	Country	Study design	Sample size	Study groups	Onset age (median/mean)	Main results
Goules *et al*. 2020[6]	Greece and Italy	Case-control study	1997	YopSS (≤35 y) EopSS (≥65 y) Middle-aged control (40–50 y)	YopSS: 29 (5–35) EopSS: 69 (65–88)	EopSS had a higher frequency of salivary gland enlargement, lymphadenopathy, Raynaud's phenomenon, haematologic and immunologic disorders, and lymphoma, while EopSS had more frequency of dry mouth, ILD, and lymphoma compared to middle-aged controls, respectively.
Botsios *et al*. 2011[7]	Italy	Retrospective study	336	YopSS (≤40 y) AopSS (>40 and ≤65 y) EopSS (>65 y)	YopSS: 28.5 ± 9.9 AopSS: 51 ± 6.7 EopSS: 72.9 ± 3.8	No statistical difference was found among the three groups in terms of glandular and extra-glandular manifestations, haematologic and immunologic disorders.
Lee *et al*. 2021[13]	Korea	Two-centre prospective study	221	YopSS (<40 y) AopSS (≥40 and <65 y) EopSS (≥65 y)	YopSS: 33 (29-39) AopSS: 53 (46.5-59) EopSS: 70 (68-75)	EopSS had a higher prevalence of ILD, less arthritis, lower positivity of anti-SSA and anti-SSB, and lower levels of RF, complement 4, and immunoglobulin G.
Tishler *et al*. 2001[14]	Israel	Monocentric cohort study	85	YopSS (<65 y) EopSS (>65 y)	YopSS: 43 (20–64) EopSS: 71 (66–80)	RF and anti-SSA antibodies were more common in YopSS. No significant difference was noted in clinical manifestations between the two groups.
Ramos-Casals *et al*. 1998[15]	Spain	Retrospective study	144	YopSS (<35 y) EopSS (>35 y)	Total: 53 (20–87) YopSS: 28 (20–34)	YopSS had higher prevalence of lymphadenopathy, RF, hypergammaglobulinemia, and lymphoproliferative disease.
Garcia-Carrasco *et al*. 2002[16]	Spain	Cohort study	400	YopSS (<35 y) EopSS (>70 y)	Total: 52.7 ± 0.85	YopSS demonstrated higher prevalence of fever, lymphadenopathy, and anti-SSA antibodies compared with those having disease onset after 35 years; EopSS showed no difference in clinical characteristics compared with those having disease onset before 70 years.
Garcıá-Carrasco *et al*. 1999[17]	Spain	Prospective study	223	YopSS (<70 y) EopSS (≥70 y)	Total: 53 (15–87) EopSS: 74 (70–87)	There was no difference in the prevalence of clinical manifestations and immunological features between YopSS and EopSS.

All values of onset age are presented as mean (standard deviation) or median (interquartile range).
YopSS: young-onset pSS; AopSS: adult-onset pSS; EopSS: elderly-onset pSS; ILD: interstitial lung disease; RF: rheumatoid factor.

ti-SSA (p_{trend} <0.001), anti-SSB (p_{trend} <0.001), anti-Ro52 (p_{trend} =0.005), and RF (p_{trend} <0.001) positivity tended to decrease with an increase in onset age, but anti-CENPB (p_{trend} =0.014) positivity demonstrated opposite trend (p_{trend} <0.001) (Fig. 2B-D). Moreover, the proportion of hyper-IgG (p_{trend} =0.022) also tended to decrease with the increase of onset age (p_{trend} <0.001) (Fig. 2B). No difference was detected in terms of anaemia and elevated ESR in the LLA test.

Review of the literature

Up to now, seven studies defining onset age as the time of pSS occurrence investigated the clinical characteristics of pSS with different onset age (Table III) (6, 7, 13-17). Among the studies, two were from Asian countries (Korea and Israel) (13, 14) and the remaining five were from Europe (6, 7, 15-17). Four studies (14-17) compared the clinical features of either YopSS or EopSS to the rest of the study population, only two (7, 13) evaluated differences among YopSS, AopSS, and EopSS groups. A case-control study (6) included 1997 patients with pSS, comparing YopSS and EopSS with controls whose age of pSS onset was within the typical 4th or 5th decade of life. One of the seven studies (13) performed multiple comparisons during data analysis, but none mapped the variation tendency of phenotypes along the onset age of pSS.

The mean age at onset of pSS were similar to those in most previous studies (6, 7, 13, 15-17), no matter in the whole population, YopSS group, AopSS group, or EopSS group. Three of the seven studies (6, 15, 16) suggested that YopSS demonstrated higher proportions in haematologic and immunologic disorders, compared to EopSS. Two studies (6,13) showed that EopSS had a higher prevalence of ILD but fewer immunologic disorders. One study (14) reported that EopSS had less RF and anti-SSA positivity but similar clinical manifestations, when compared with younger pSS. Two studies (16,17) reported that there was no difference in clinical characteristics including immunologic disorders between EopSS and younger ones. What's more, an Italian retrospective study (7) divided pSS patients into three age groups concluded that there was no difference among the three groups in

glandular manifestations, ILD, haematologic and immunologic disorders. In summary, the influence of onset age on clinical phenotypes in patients with pSS is controversial.

Discussion

This is the well-designed, largest retrospective study to investigate the clinical characteristics of pSS patients with distinct onset ages in China. In order to get comprehensive and reliable results, this work considered three distinct onset age groups (YopSS, AopSS, and EopSS), performed multiple comparisons, and explored the variation tendency of phenotypes for the first time. Although the impact of onset age on clinical phenotypes of pSS has been studied in the past, the impact is not fully understood due to the controversial results. The major findings of this study can be summarised as follows: a) YopSS demonstrated more immunologic disorders but less dryness and ILD; b) the prevalence of dryness and ILD tended to increase with the increase of onset age; c) the proportions of leukopenia, low C3, low C4, and ANA, anti-SSA, anti-SSB, and RF positivity tended to decrease with an increase in onset age.

Differences in clinical manifestations

A previous case-control study (6) showed that dry mouth is more common in EopSS than in AopSS. Another prospective study (13) indicated that arthritis is less common in EopSS than in YopSS and AopSS. Our study confirmed that YopSS was associated with lower prevalence of dry mouth and xerophthalmia, and the proportion of dryness tended to increase with the increase of onset age; fatigue and arthralgia were more common in AopSS than in YopSS and EopSS, respectively; EopSS was associated with a lower prevalence of dental caries, and dental caries showed a downward trend with the increase of onset age. All these findings provide evidence of distinct clinical manifestations in pSS patients with different age of onset.

ILD is the most common pulmonary manifestation and a vital cause of death in patients with pSS (21). A Korean prospective study (13) reported the prevalence of ILD in overall pSS patients, YopSS, AopSS, and EopSS to be 19.5%, 8.7%, 13.5%, and 51.2%, respectively; patients with EopSS were more prone to develop ILD. A European case-control study (6) found a higher prevalence of ILD in EopSS (7.9%) than in AopSS (2.5%). However, two other European studies showed a lower prevalence of ILD in pSS patients, at 1.2% (7) and 8.5% (17), and detected no difference among the groups. The overall prevalence of ILD in our study was 34.6%. Current evidence regarding the prevalence of pSS-ILD is controversial (22). However, its prevalence appears to be higher in China than in Europe (22-25). A study has suggested that pSS patients from different ethnicities and locations have a distinct genetic susceptibility locus, which may modulate the clinical phenotypes (26). Therefore, the heterogeneity in ILD prevalence among different studies may be partially attributed to the differences in ethnicities and locations. Our data showed that EopSS was more commonly associated with ILD, and the prevalence of ILD tended to increase with increase of onset age. This result is consistent with findings of a previous international study, which included 12,753 pSS patients from 25 countries and showed that the frequency of pulmonary involvement tended to increase with increase of age at disease diagnosis (27). Two recent studies suggested that aging and male sex were risk factors for pSS-ILD (22, 28). Our results indicated that the EopSS group had higher proportions of male patients. All of these confirmed the association of elderly onset age with prevalence of ILD in patients with pSS, and EopSS also merits closer follow-up and regular monitoring.

Differences in laboratory indicators

Patients with YopSS generally demonstrated more immunological manifestations such as anti-SSA and RF positivity and lower levels of C4, however, EopSS demonstrated lower biological activity (6, 13-16). Similarly, our study identified YopSS to be associated with higher proportions of leukopenia, low C3, low C4, and ANA, anti-SSA, anti-SSB, and RF positivity. Notably, the prevalence of these immunologic disorders showed downward trends with the increase of onset age. However, two previous studies (7, 17) detected no notable differences in immunological characteristics among distinct onset age groups. Based on findings from most current studies, it appears reasonable to conclude that onset age can modulate serological manifestations of pSS. In this context, YopSS requires regular monitoring for blood cells and complements. It has been reported that the risk of B-cell lymphoma is approximately 20 times as high among patients with pSS as in the general population (1). The prolific serologic profile of YopSS could imply a robust B cell responsiveness, which could be associated with a higher probability for future lymphoma development (29). More studies are needed to confirm this. Due to the low positivity of autoantibody in elderly patients with features strongly suggestive of pSS, MSG biopsy is more likely to be the only way to confirm the diagnosis of pSS.

Of note, our results showed that the onset preceded the diagnosis by 6 years in pSS, which was similar to previous studies (6, 7). Future studies are needed to determine whether the delay in diagnosis affects the phenotypic presentation of the disease. Additionally, the median age at diagnosis of pSS in this study was higher than that reported in some other studies (30), which may be partially attributed to differences in ethnicity. It would be interesting to validate the role of ethnicity on clinical phenotypes of pSS in future.

Limitations

This study has several limitations. First, this is a single-centre retrospective study enrolling 742 Chinese patients with pSS. Some potential confounders may be unknown although we performed Bonferroni adjustment for multiple comparisons to obtain reliable results. Our findings provide a better understanding of the influence of onset age on clinical phenotypes in Chinese patients with pSS, but the results may not be generalised to all ethnicities. Second, the date of pSS onset may be subject to recall bias. Thus, we recorded age of onset in years and divided data into three age groups for analysis to avoid discrepancies. Third, we can-

not analyse all clinical manifestations of pSS such as Raynaud's phenomenon and the patterns of ILD, because relevant data was missing in the medical records. Multi-centre prospective studies with long-term follow-up are needed to supplement and validate our findings.

Conclusions

Approximately one third of pSS patients had early and late disease onset. YopSS was associated with less dryness, but more hypocomplementaemia, and ANA, anti-SSA, anti-SSB, and RF positivity. The prevalence of dryness and ILD tended to increase with increase in onset age. However, the proportions of leukopenia, low C3, low C4, and ANA, anti-SSA, anti-SSB, and RF positivity demonstrated opposite trends.

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