RHEUMATOLOGY

Rheumatology 2022;61:597–605
doi:10.1093/rheumatology/keab367
Advance Access publication 20 April 2021

Original article

Patients with early-onset primary Sjögren's syndrome have distinctive clinical manifestations and circulating lymphocyte profiles

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Abstract

Objectives. To further investigate the clinical characteristics and circulating lymphocyte profiles of patients with early-onset primary Sjögren's syndrome (pSS).

Method. Data of 333 patients with pSS were analysed retrospectively. Early onset was defined as a pSS diagnosis at an age of 35 years or younger. The clinical, laboratory and immunophenotypic profiles of peripheral blood lymphocyte subsets were compared between early- and later-onset pSS.

Results. Thirty-six (10.81%) patients matched the definition of early-onset pSS, with age at disease onset being 28.97 (5.53) years. Elevated serum IgG level (77.14% *vs* 31.16%, $P < 0.001$), low C3 (41.67% *vs* 20.20%, $P = 0.004$) and C4 levels (27.78% *vs* 6.40%, $P < 0.001$), anti-SSA positivity (91.67% *vs* 51.85%, $P < 0.001$) and anti-SSB positivity (50% *vs* 20.54%, $P < 0.001$) were more frequent in early-onset patients. The frequencies of hematological (80.56% *vs* 52.53%, $P = 0.001$), renal (19.44% *vs* 5.05%, $P = 0.005$) and mucocutaneous involvement (50% *vs* 22.56%, $P < 0.001$) were significantly higher in the early-onset pSS group, which showed a higher 2010 EULAR SS Disease Activity Index (ESSDAI) [11(6.25–17) *vs* 7(3–12); $P = 0.003$], compared with the later-onset group. In addition, profound $CD4^+$ T-cell lymphopenia was found in patients with early-onset.

Conclusions. Patients with early-onset pSS have distinctive clinical manifestations and greater activation of the cellular immune system, present with more severe clinical symptoms and immunological features, have increased activation of circulating T cells and have an unfavourable prognosis. Thus, they require more positive treatment with glucocorticoids and/or immunosuppressants and merit closer follow-up and regular monitoring.

Key words: primary Sjögren's syndrome, onset age, prognoses, ESSDAI, lymphocyte profile

CLINICAL SCIENCE

Rheumatology key messages

- Early-onset pSS patients have distinctive clinical manifestations and greater activation of the cellular immune system.
- Early-onset pSS patients exhibit a higher intensity of the disease (as evaluated by ESSDAI).
- Patients with early-onset pSS need more positive treatment and closer follow-up.

Introduction

Primary Sjögren syndrome (pSS) is a chronic systemic rheumatic disease characterized by lymphoplasmacytic infiltration of the salivary and lachrymal glands,

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Submitted 24 February 2021; accepted 14 April 2021

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presenting as sicca syndrome [1]. pSS can affect virtually all organs, ranging from mild inflammatory arthralgia to life-threatening manifestations such as pulmonary interstitial fibrosis or nervous system involvement [2, 3]. Therefore, a different therapeutic strategy based on both the sicca and systemic manifestations of patients with pSS should be considered.

pSS is a common disorder that affects 0.1% to 4.8% of the general population. pSS can occur in people of all ages, but it most frequently affects women between the fourth and sixth decades of life, with a female to male ratio of 9:1 [4, 5]. The heterogeneous presentation of autoimmune diseases (including RAs, SLE and pSS) has encouraged the investigation of subsets of patients with specific features, courses and outcomes. Previous studies have attempted to determine whether age at onset is associated with a particular expression in different autoimmune diseases. Patients with early-onset RA have been found to be less active and suffer from more disabilities [6]. Patients with early-onset SLE had a higher SLE Disease Activity Index 2000 and more renal features, neurologic manifestations and immunologic abnormalities than those with late-onset SLE [7]. It is of great clinical importance to investigate the effect of age at onset, as it may affect the clinical progress of pSS. However, early-onset pSS appears to be less frequent, with an incidence ranging from 11.4% to 19%, and only a few studies have so far focussed on the relationship between the clinical and laboratory findings and age at onset in pSS patients [8–11]. Further, the existing data on his issue are controversial. Moreover, information on early-onset pSS in northeast Asia, and specifically China, is limited.

To better understand whether any relationship exists between disease manifestations and age at onset in Chinese pSS patients, this retrospective study enrolled 333 consecutive, newly-diagnosed pSS patients. The demographic data, immune serological features, clinical profiles, disease activity and different treatment modalities in patients with early-onset pSS and those with late-onset pSS were analysed and compared. In the present study, we aimed to seek evidence for the greater immune disturbance in patients with early-onset pSS. For that purpose, the distribution of various lymphocyte subsets in the peripheral blood of different age-onset pSS patients was investigated. The patients were also followed up and their prognoses were evaluated.

Materials and methods

Patients

A monocentric retrospective study was carried out, and 333 newly diagnosed pSS patients treated at the Department of Rheumatology of Hebei General Hospital between September 2016 and February 2019 were included. All subjects with pSS were classified according to the American-European Consensus Group classification criteria of 2002(2). Those who did not have chronic hepatitis C virus human immunodeficiency virus infection, previous lymphoproliferative processes and associated systemic autoimmune diseases (such as RA, SLE, systemic sclerosis, *et al.*) were enrolled in the study. All included patients had an Asian phenotype. The enrolled pSS patients were divided into two groups based on whether they had been diagnosed with pSS when they were $\leq$35 years old (early onset) or older than 35 years (later onset). All study participants provided written informed consent, and the study design was approved by the Ethics Board of Hebei General Hospital (approval ID: NO.2016070).

Clinical variables

The clinical and laboratory variables of pSS patients at onset, before starting any treatment, were retrospectively reviewed. The levels of biological parameters were recorded from the case files and included data on ESR, CRP, immunoglobulins (IgG, IgA, and IgM), complement (C3 and C4), blood protein electrophoresis, RF and antinuclear antibodies (ANAs). All tests were performed at the clinical laboratory and all data were available. Clinical features rigorously assessed included age at diagnosis, disease duration and clinical manifestations. Extraglandular involvement was evaluated according to the 2010 EULAR SS Disease Activity Index (ESSDAI) [12, 13]. Mucocutaneous involvement was defined as cutaneous vasculitis (demonstrated by cutaneous purpura and skin biopsy); digestive involvement was defined as the appearance of symptoms and signs associated with impaired digestive function, including oesophageal impairment, gastroesophageal reflux, altered liver function tests and/or abnormal liver biopsy. The ESSDAI as assessed to measure disease activity at diagnosis and at last follow-up. Disease activity was defined as low, moderate and high, with scores of $<$5, 5–13 and $\geq$14, respectively [14]. Clinical and laboratory data were collected and according to a standard protocol [15].

The duration of follow-up was defined as the interval from diagnosis until the date of the latest data collection (January 2021) or the date of death. Patients were usually evaluated every 3 or 6 months based on clinical judgement. Information regarding vital signs and causes of death was obtained from medical records.

Cell surface staining and flow cytometric analysis

Fluorescence-activated cell sorting (FACS) analysis of lymphocyte subsets was performed according to a standard protocol before any treatment. In brief, erythrocytes were lysed, and cells were harvested and washed twice and stained for 20 min at 4°C using specific antibodies. Cells were incubated with antibodies against CD3, CD4, CD8, CD16, CD56, CD45 and CD19 (all Becton Dickinson, San Diego, CA, USA) and subsequently washed and resuspended in phosphate-buffered saline prior to analysis. The stained cells were measured with a FACS Canto flow cytometer (Becton Dickinson,

San Jose, CA, USA) and the data were analysed using FlowJo Software (Treestar, Ashland, OR, USA).

Statistical analysis

Statistical analysis was carried out using SPSS 25.0 (IBM, Armonk, NY, USA). The chi-squared test or Fisher's exact test was used for comparisons, and categorical data are summarized using frequencies and percentages. The quantitative data are presented as means (S.D.) when normally distributed and as medians and interquartile ranges (IQR) when not normally distributed. In the between-group comparisons, the quantitative data were analysed using Student's *t test* or the Mann–Whitney *U* test as appropriate. The correlations between variables were evaluated with Spearman's rank correlation coefficient. $P < 0.05$ was considered significant.

Results

Demographic data

In total, 333 patients with pSS were enrolled in this study, with more female than male patients (310 *vs* 23). Although the predominance of females among those with early-onset pSS [35 of 36 (97.2%)] was higher than that observed in later-onset pSS [275 of 297 (92.5%)], the difference did not reach statistical significance ($P = 0.49$). The median (IQR) age at disease diagnosis was 29 (26–33) years in the early-onset group. Furthermore, disease duration was shorter in the early-onset pSS group ($P < 0.001$) (Table 1).

Laboratory characteristics

As shown in Table 1, a lower haemoglobin level [113.5 (102.25–121.75) g/l *vs* 123 (111–133) g/l, $P = 0.001$], higher serum IgG level [21.7 (19.2–30.58) g/l *vs* 14.9 (12–18.30) g/l, $P < 0.001$], and higher serum RF level [56.40 (17.0–218) IU/l *vs* 14.60 (10.6–56.75) IU/l, $P < 0.001$] were observed in the early-onset group. An elevated serum IgG level (77.14% *vs* 31.16%, $P < 0.001$), low C3 level (41.67% *vs* 20.20%, $P = 0.004$), low C4 level (27.78% *vs* 6.40%, $P < 0.001$), RF positivity (74.29% *vs* 44.93%, $P = 0.001$), anti-Ro52 positivity (88.89% *vs* 56.57%, $P < 0.001$), anti-RNP positivity (27.78% *vs* 9.76%, $P = 0.004$), anti-Ro/SSA positivity (91.67% *vs* 51.85%, $P < 0.001$) and anti-La/SSB positivity (50% *vs* 20.54%, $P < 0.001$) were more frequently observed in patients with early-onset disease. In addition, there was no between-group difference regarding the presence of a monoclonal peak ($P = 0.99$). Moreover, the positive ANA rate was not significantly different between the two groups. Similarly, platelet counts, CRP value and anti-ACA positivity did not significantly differ between the groups at the time of diagnosis. Meanwhile, a focus score of ≥ 1 at histological evaluation of the minor salivary gland showed no between-group difference (Table 1).

Clinical manifestations

When we evaluated the clinical findings at the time of pSS diagnosis (Fig. 1 and Supplementary Table 1, available at *Rheumatology* online), the frequencies of hematological (80.56% *vs* 52.53%, $P = 0.001$), renal (19.44% *vs* 5.05%, $P = 0.005$) and mucocutaneous (50% *vs* 22.56%, $P < 0.001$) involvement were significantly higher in the early-onset group. There was no significant difference in terms of xerostomia, xerophthalmia, arthritis, pulmonary involvement, nervous system involvement or digestive system involvement between the two groups.

Lymphocyte subset distribution in the peripheral blood of patients with early- and later-onset pSS

Patients with early-onset pSS had a significantly lower number of circulating lymphocytes compared with those in the later-onset group [1.22 (1.00–1.59) $\times 10^9$/l *vs* 1.52 (1.12–1.89) $\times 10^9$/l, $P = 0.03$]. We further conducted immune phenotyping of different age-onset pSS patients with flow cytometry to investigate their immunological status. The distributions of T cells, B cells and NK cells in patients with early-onset and later-onset disease are shown in Fig. 2 and Supplementary Table 2, available at *Rheumatology* online. We found a significance decrease in absolute numbers of CD16/CD56$^+$ NK cells in early-onset patients [106.18 (78.65–135.66)/ul *vs* 192.01 (128.40–297.81)/ul, $P < 0.001$], whereas CD3$^+$ T cells and CD19$^+$ B cells were comparable between the groups ($P > 0.05$). Because lymphopenia was mostly the result of T cell deficiency, we performed a further sub-analysis of T cells and observed a more pronounced reduction of CD4$^+$ T cells compared with their CD8$^+$ counterparts. The between-group comparison revealed that profound CD4+ T cell lymphopenia and decreased numbers of CD16/CD56$^+$ NK cells were the most distinguishing features of the early-onset group. Besides, the ESSDAI inversely correlated with the absolute number of CD3$^+$ T cells, CD4$^+$ T cells, CD19$^+$ B cells and CD16/CD56+ NK cells.

Disease activity, treatment and prognosis

Patients with early-onset disease showed a higher ESSDAI [11 (6.25–17) *vs* 7 (3–12); $P = 0.003$]. Most of the patients (52.78%) in the early-onset group had moderate disease activity at diagnosis of pSS; 11.11% had low disease activity, and 36.11% had high disease activity. These values were significantly different in the later-onset pSS group (46.46%, 30.30% and 23.23%, respectively, $P = 0.01$).

Regarding therapy, prednisone/methylprednisolone were more often prescribed in the early-onset group (38.89% *vs* 21.55%, $P = 0.02$). Immunosuppressive therapy was started in 19/36 patients; 10 were treated with leflunomide, five with mycophenolate mofetil, two with iguratimod, one with ciclosporin A and one with cyclophosphamide. When compared with the later-onset group, more patients in the early-onset group received

Table 1 Baseline demographic and laboratory characteristics of the groups according to age at pSS diagnosis

	Early-onset group ($n = 36$)	Later-onset group ($n = 297$)	*P*-values
Demographic characteristics			
Sex(F/M)	35:1	275:22	0.49
Age at onset, years	28.97 (5.53)	56.95 (10.65)	< 0.001
Disease duration, months	24 (4–45)	60 (12–120)	< 0.001
Laboratory findings			
WBC ($\times 10^9$/l)	4.72 (3.72–6.55)	4.96 (3.97–6.24)	0.81
Neutrophil count ($\times 10^9$/l)	3.65 (2.08–4.73)	2.93 (2.19–4.17)	0.49
Lymphocyte count ($\times 10^9$/l)	1.22 (1.00–1.59)	1.52 (1.12–1.89)	0.03
Haemoglobin ($\times$g/l)	113.5 (102.25–121.75)	123 (111–133)	0.001
Platelet counts ($\times 10^9$/l)	240 (159.5–298)	223 (179–264.5)	0.49
NLR	2.73 (1.67–3.51)	1.98 (1.41–2.83)	0.05
PLR	161.83 (118.76–269.34)	143.14 (109.65–197.07)	0.07
ESR (mm/1h)	26 (15–51)	17 (8–35)	0.01
CRP (mg/l)	1.94 (0.52–11.91)	3.30 (1.24–4.18)	0.31
RF (IU/l)	56.40 (17.0–218)	14.60 (10.6–56.75)	< 0.001
IgG (g/l)	21.7 (19.2–30.58)	14.9 (12–18.30)	< 0.001
IgA (g/l)	3.0 (2.4–4.14)	2.73 (1.91–3.53)	0.19
IgM (g/l)	1.24 (0.9–1.64)	1.14 (0.79–1.61)	0.19
C3 (g/l)	0.93 (0.82–1.11)	1.08 (0.93–1.21)	0.001
C4 (g/l)	0.17 (0.10–0.20)	0.20 (0.16–0.24)	0.001
Elevated ESR (*n*, %)	22, 62.86%	129, 45.10%	0.05
Elevated CRP (*n*, %)	10, 28.57%	53, 19.06%	0.15
Hyper-IgG (*n*, %)	27, 77.14%	91, 31.16%	< 0.001
Monoclonal peak (*n*, %)	1/34, 2.94%	7/242, 2.89%	0.99
Low C3 (*n*, %)	15, 41.67%	60, 20.20%	0.004
Low C4 (*n*, %)	10, 27.78%	19, 6.40%	< 0.001
RF (+) (*n*, %)[a]	26, 74.29%	124, 44.93%	0.001
ANA (+) (*n*, %)[b]	32, 88.89%	231, 77.78%	0.12
Anti-RNP (+) (*n*, %)	10, 27.78%	29, 9.76%	0.004
Anti-Ro52 (+) (*n*, %)	32, 88.89%	168, 56.57%	< 0.001
Anti-Ro/SSA (+) (*n*, %)	33, 91.67%	154, 51.85%	< 0.001
Anti-La/SSB (+) (*n*, %)	18, 50%	61, 20.54%	< 0.001
Anti-ACA (+) (*n*, %)	1, 2.78%	44, 14.81%	0.05
Pathological MSG with focus score ≥ 1 (*n*, %)	36, 100%	273, 95.12%	0.38
ESSDAI	11 (6.25–17)	7 (3–12)	0.003

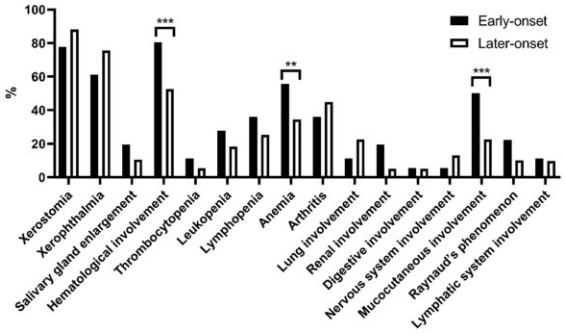
Values are presented as *n*, mean (S.D.), median (interquartile range) or number (%). All *P*-values were evaluated by comparing between the patients with early-onset and those with later-onset disease using the chi-squared test, Fisher's exact test, Student's *t test* or Mann–Whitney's *U* test, as appropriate. ACA: anti-centromere antibodies; ANA: antinuclear antibodies; IgA: immunoglobulin IgA; IgG: immunoglobulin IgG; IgM: immunoglobulin IgM; MSG: minor salivary gland; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; pSS: primary Sjögren's syndrome.
[a]positive RF >20 IU/ml; [b]positive for ANA titres ≥1:320.

mycophenolate mofetil (13.89% *vs* 0.34%, $P < 0.001$). Therapy did not differ between the two groups regarding other immunosuppressants (Supplementary Table 3, available at *Rheumatology* online).

The two groups of patients had a similar duration of follow-up [30.06 (8.65) months *vs* 33.02 (8.94) months, $P = 0.33$]. At the last follow-up visit, the ESSDAI in patients with early-onset was still higher than that in patients with later-onset patients [6 (2–10) *vs* 5 (0–8); $P = 0.02$], which was significantly lower compared with the ESSDAI at diagnosis ($P < 0.001$). Moreover, disease activity was low in 9/35 (25.71%) patients, moderate in 24/35 (68.57%), and high in 2/35 (5.71%). Improvement in the ESSDAI at the last follow-up visit, compared with that at baseline, was also observed in the later-onset group [5 (0–8) *vs* 7 (3–12); $P < 0.001$], and disease activity was low in 133/278 (47.84%), moderate in 119/278 (42.81%) and high in 26/278 (9.35%) patients (Fig. 3 and Supplementary Table 4, available at *Rheumatology* online).

During follow-up, more pSS patients developed SLE in the early-onset group (2.78%) than in the later-onset group (1.74%), although the difference was not statistically significant ($P = 0.51$). Besides, no patient was diagnosed with lymphoma or other malignancies during the follow-up. Finally, four patients (1.20%) in later-onset group died; death was due to pSS complications in one of these patients.

FIG. 1 Clinical manifestations of the two groups of patients according to age at pSS diagnosis

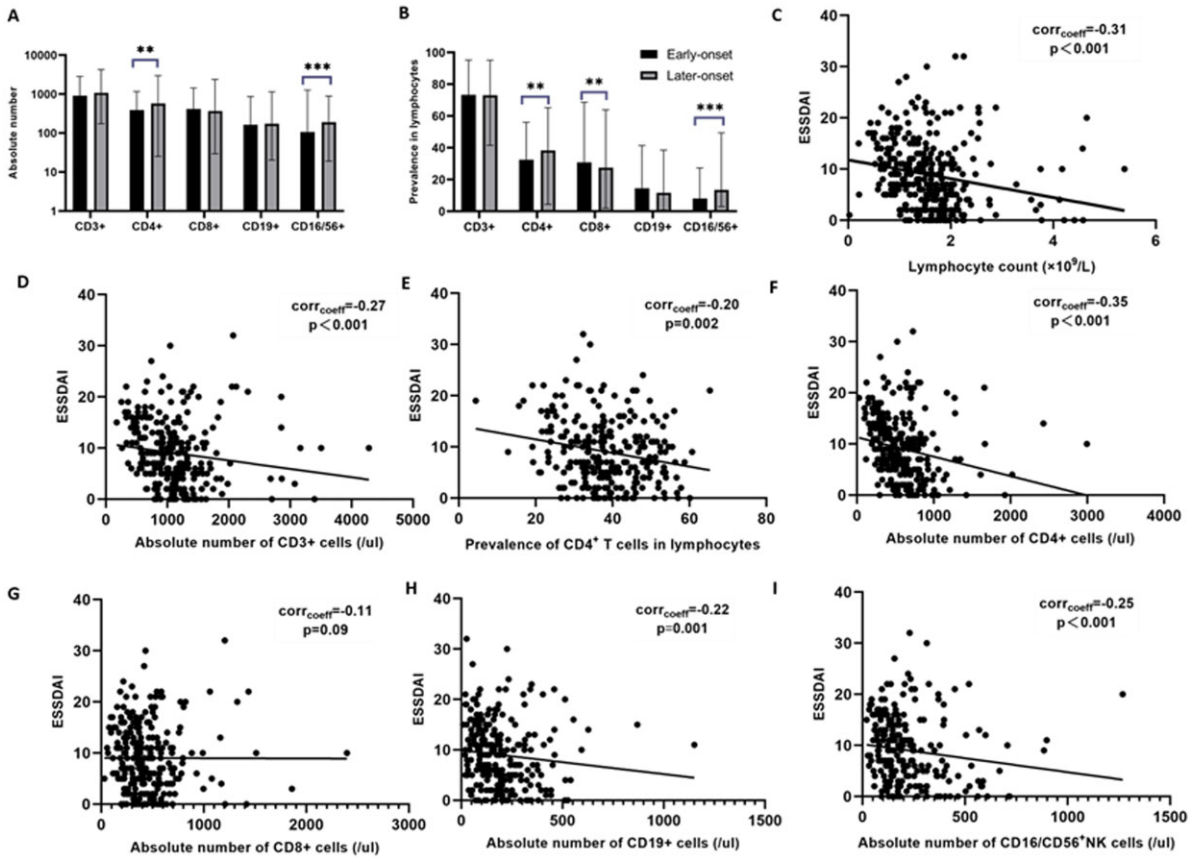


**P <0.01, ***P <0.001.

Discussion

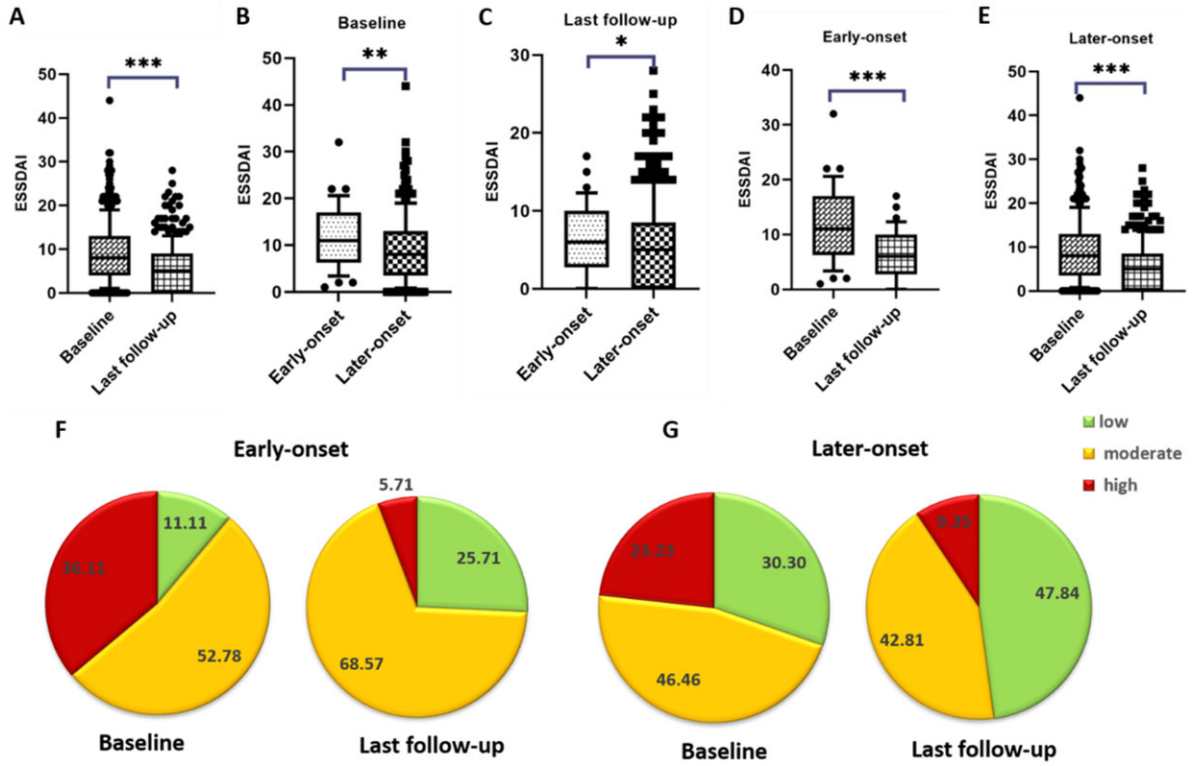
It is well known that pSS is a heterogeneous entity with geographic/ethnic origin, genetic, environmental and socioeconomic variations, which may drive the different biological and immunological responses. To date, studies investigating the prognostic factors of early-onset pSS have centered on the clinical and laboratory features at diagnosis. The present study was the first to evaluate the differences between patients with early-onset and later-onset pSS in China. Our study uncovered that patients with early-onset pSS had distinctive demographic features and circulating lymphocyte profiles; they presented with more severe clinical symptoms and immunological features than those with later-onset. Our findings also suggested that patient with early-onset pSS should be monitored regularly because of their potential to develop SLE.

FIG. 2 Immunological status in patients with early-onset pSS



Graphs show (**A**) absolute numbers of $CD3^+$ T cells, $CD4^+$ T cells, $CD8^+$ T cells, $CD19^+$ B cells and CD16/CD56+ NK cells in the early-onset and later-onset groups; (**B**) prevalence of $CD3^+$ T cells, $CD4^+$ T cells, $CD8^+$ T cells, $CD19^+$ B cells and CD16/CD56+ NK cells in the lymphocytes of the early-onset and later-onset groups; (**C**) correlation of the ESSDAI with lymphocyte count in pSS patients; (**D**) correlation of the ESSDAI with absolute numbers of $CD3^+$ T cells in pSS patients; (**E**) correlation of the ESSDAI with the prevalence of $CD4^+$ T cells in the lymphocytes of pSS patients; (**F**, **G**, **H**, **I**) correlation of the ESSDAI with the absolute numbers of $CD4^+$ T cells, $CD8^+$ T cells, $CD19^+$ B cells and CD16/CD56+ NK cells in pSS patients. Lines between bars indicate significantly altered fractions. **P<0.01, ***P<0.001.

FIG. 3 Disease activity of patients with pSS as grouped by age of onset at baseline and at the last follow-up visit



Graphs show the ESSDAI (**A**) at baseline and at the last follow-up visit for all patients, (**B**) between the early-onset group and later-onset group at baseline, (**C**) between early-onset group and later-onset group at the last follow-up visit, (**D**) at baseline and at the last follow-up visit for the early-onset group, and (**E**) at baseline and at the last follow-up visit for the later-onset group. Graphs show the improvements of disease activity at baseline and at the last follow-up visit (**F**) in those with early-onset patients and (**G**) with later-onset patients. *$P<0.05$, **$P<0.01$, ***$P<0.001$.

Our study found that patients with early-onset had distinctive demographic features; they had a significantly shorter disease duration than those with later-onset. Moreover, a strikingly more severe disease activity characterized early-onset pSS disease, with the frequencies of hematological, renal and mucocutaneous involvement (80.56%, 19.44% and 50%, respectively) being significantly higher than those in the later-onset group. In a previous study on a Spanish cohort of 144 patients with 13 patients <35 years old, the early-onset group had a higher prevalence of articular involvement (31%), peripheral neuropathy (23%), cutaneous vasculitis (23%) and RP (23%) [8]. Anquetil *et al.* investigated 395 consecutive patients with pSS recruited from a French nationwide multicentre prospective cohort including 55 patients with early-onset disease. These patients presented a significantly higher frequency of salivary gland enlargement (SGE) (47.2%), adenopathy (25.5%), purpura (23.6%) and renal involvement (16.4%) than patients who at disease diagnosed age >35 years [9]. Another retrospective study of a multicentre population of 1997 consecutive pSS patients, including Italians and Greeks, showed that patients with early-onset pSS presented more frequently with SGE (39.1%), lymphadenopathy (20.7%) and Raynaud's phenomenon (36.6%) [8]. The immunological profile of early-onset pSS highlights the presence of anti-SSA and anti-SSB antibodies, RF positivity, low C3 and C4 levels and hypergammaglobulinemia. Similar findings have been described by previous groups [8–10]. Although they shared some common features, patients from different ethnic groups included in the early-onset pSS group did not all present with the same manifestations, suggesting that genetic, environmental and socioeconomic variations are involved in the biological and immunological responses.

A previous study suggested that peripheral lymphopenia was associated with higher disease activity and mortality in pSS patients [16]. In the present study, for the first time, we compared the distribution of circulating lymphocyte subsets in different age-onset patients with pSS. In this study, we found that patients with early-onset pSS had a significantly reduced lymphocyte count compared with those in the later-onset group. A lower number of T cells was more pronounced in the early-onset group and could be explained by profound $CD4^+$ T-cell lymphopenia. This may partly shed light on the reason behind the marked disturbances in the

serological aspects of the early-onset group, as systemic immune activation results in increased levels of circulating autoantibodies and immune complexes and a severe inflammatory condition. The main reason for the marked $CD4^+$ T-cell lymphopenia in different age-onset pSS patients needs to be further studied. Interestingly, we also found CD16/CD56+ NK cells, innate lymphoid cells that exhibit a potential regulatory role in exocrine gland tissues and the peripheral blood of pSS disease [17, 18] were significantly decreased in the early-onset group. Our data provide evidence that the immunological status may contribute to the distinct features of different age-onset pSS patients.

SLE and pSS have several similar clinical and serological aspects [19–22], which often hamper distinguishing between the two disorders [23]. Recent studies have suggested that both disorders share many etiopathogenic links, including genetic factors [24–26], epigenetic alterations [26] and activation of T and B cells [22]. Conversely, previous studies have reported that patients with early-onset pSS are more likely to develop SLE than those with later-onset pSS. In a retrospective study investigating 55 SS/SLE patients attending the Department of Rheumatology of Peking Union Medical College Hospital, Yang *et al.* revealed that compared with the control pSS group, SS/SLE patients had a younger age at onset [31 (12) *vs* 39 (11) years, $P = 0.001$] [27]. These results suggested that long-term observation is required because patients with early-onset pSS have the potential to develop SLE.

Mortality in pSS cohorts is mainly attributed to systemic disease and lymphoma [28, 29]. In light of the current data, systemic involvement, present in almost 70–80% of the patients at diagnosis, plays a key role in the prognosis of pSS. Brito-Zeron *et al.* evaluated the potential association between baseline systemic activity and mortality using the ESSDAI for the first time and suggested that high baseline systemic activity may be related to a higher risk of death [16]. In addition, disease activity also played a role in the development of lymphoma [30]. In our study, the early-onset group showed a significantly higher ESSDAI. In contrast, clinical predictors for the development of lymphoma [31, 32] (lower age at diagnosis, positive RF, anti-Ro/SSA positivity, hypocomplementemia and hyperglobulinemia) were also more common in the early-onset pSS group. These features further support the theory that in early-onset pSS, patients have a higher frequency of lymphoproliferative disease development and mortality.

Overall, after a more intensive treatment, systemic disease activity significantly decreased over time in patients with early-onset, with ~90% of patients retaining low and moderate disease activity at the last follow-up. Therefore, better disease stratification is warranted. Patients who are at higher risk for a worse outcome must be identified and receive more vigorous treatment for disease improvement.

This study had several limitations. First, the retrospective nature of the data comprises an important limitation that may have affected the conclusions. Information on the cryoglobulin status was insufficient because of the lack of routine evaluation of cryoglobulin in our patients. In addition, the heterogeneity of Chinese pSS patients, possibly because of genetic and environmental differences, is another limitation that may have also affected the data analysis. Finally, patients from a single centre were enrolled, which may have led to selection bias.

Conclusions

In conclusion, our study showed that unlike patients with later-onset pSS, those with early-onset pSS have distinctive clinical manifestations and greater activation of the cellular immune system, present with more severe clinical symptoms and immunological features, have increased activation of circulating T and B cells, and have a worse prognosis. Therefore, they require more intensive treatment with glucocorticoids and/or immunosuppressants and stricter monitoring.

Acknowledgement

The authors would like to thank Dr Wang Zhihua for excellent flow cytometry work.

Author Contributions: Conceptualization: L.W., Z.F., N.X. and Z.W.; investigation: X.Z., L.M., S.Y. and R.X.; resources: G.S., Y.L.; writing: L.W., C.J., L.Ya., and L.Yi.; supervision: Z.F., S.L.; funding acquisition: L.W. All authors have read and agreed to the published version of the manuscript.

Funding: This work was funded by the grant from the National Nature Science Foundation of China (No. 81801630) and the National Nature Science Foundation of Hebei Province (No. H2018307047).

Disclosure statement: The authors have declared no conflicts of interest.

Data availability statement

All data relevant to the study are included in the article or uploaded as online supplementary information. The data that support the findings of this study are available from the corresponding authors on reasonable request.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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