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Late-onset Sjögren disease: A different clinical entity?

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ABSTRACT

Background and aim: Sjögren's disease (SjD) exhibits heterogeneous clinical phenotypes influenced by age at onset. This study aimed to evaluate the impact of onset age on the clinical and serological characteristics of SjD in a Turkish cohort.

Methods: We retrospectively analyzed 411 patients diagnosed with SjD between 2013 and 2024, fulfilling the 2002 AECG or 2016 ACR/EULAR criteria. Patients were classified as young-onset (<40 years; YoSjD), adult-onset (40–60 years; AoSjD), or elderly-onset (>60 years; EoSjD). Demographic, clinical, laboratory, and treatment characteristics were compared among groups.

Results: The cohort comprised predominantly females (93.4%) with a median age of 55 years. RF positivity was significantly higher in EoSjS (35.5%) compared to YoSjD (27.9%) and AoSjD (19.2%, p=0.007). Inflammatory markers (ESR, CRP) were more frequently elevated in EoSjD. Interstitial lung disease (ILD) prevalence was highest in EoSjD (25.8%, p<0.05), particularly in males. Artropathy was more frequent in EoSjD (80.6%) and YoSjD (76%) than in AoSjD (64.5%, p=0.007). Anemia was more common in EoSjD (20.4%, p=0.040). Hydroxychloroquine was widely used (86.6%), with glucocorticoid and azathioprine use significantly higher in EoSjD.

Conclusions: Elderly-onset SjD demonstrates a distinct phenotype characterized by higher ILD prevalence, increased RF positivity, greater inflammatory activity, and more frequent artropathy and anemia compared to younger-onset groups. These findings highlight the need for age-tailored diagnostic vigilance, proactive ILD screening, and cautious use of immunosuppressants in older patients. Prospective multicenter studies are warranted to refine management strategies in this subgroup.

Key words: Sjögren's disease, elderly-onset, clinical and serological features, interstitial lung disease

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Background and Aim

Sjögren's disease (SjD) is a persistent autoimmune condition that predominantly impacts the exocrine glands, leading malfunction of the salivary and lacrimal glands, which results in xerostomia and keratoconjunctivitis sicca. Histopathologically, it is marked by extensive lymphocytic infiltration of the exocrine tissues. The clinical range extends beyond autoimmune exocrinopathy to encompass the musculoskeletal, respiratory, gastrointestinal, hematological, vascular, cutaneous, renal, and neurological systems(1). Cases devoid of accompanying systemic autoimmune disorders are designated as "primary" SjD(pSjD)(2). The condition primarily affects women, particularly those aged 40 to 50 years, with a female-to-male ratio of about 9/14:1(3, 4). The incidence of pSjD is typically cited as ranging from 0.5% to 1%, while certain studies have indicated rates as elevated as 6%(5-7). It is regarded as the second most prevalent rheumatic disorder following rheumatoid arthritis. Information regarding the frequency of pSjD among elderly individuals is scarce. The reported frequency varies from 1.4% to 6%, contingent upon the age barrier established for defining "elderly" and the diagnostic criteria employed(8). Recent large-scale retrospective studies have shown that the age of disease beginning considerably affects the phenotypic expression of SjD. A study involving 742 patients in China revealed that, among individuals over 65 years, the prevalence of xerostomia, abnormal Schirmer's test results, and interstitial lung disease (ILD) escalated with age, while the positivity rates for anti-SSA/SSB and rheumatoid factor (RF) significantly diminished(9). An analysis of 12,753 patients from the multinational Sjögren Big Data Consortium revealed that for each additional year at diagnosis, the prevalence of xerostomia increased by 0.13%, abnormal oral diagnostic tests by 0.11%, whereas positivity for anti-Ro, anti-La, and RF decreased by 0.57%, 0.42%, and 0.47%, respectively. The findings also emphasized a notable age-related escalation in lung involvement and peripheral neuropathy(10).The increasing recognition of late-onset SjD highlights the necessity for age-specific strategies in diagnosis and management. A thorough study published in 2025 highlighted that, in geriatric patients, diagnosis is frequently postponed because to the symptom overlap with age-related sicca complaints, polypharmacy, and comorbidities(11).This study aims to assess the impact of age at onset on the demographic, immunological, and phenotypic aspects of pSjD in a Turkish population.

Materials and Methods

Working group

Of the 462 patients diagnosed with pSjD, 26 were excluded due to loss to clinical follow-up and 25 due to missing data, resulting in a total of 51 patients excluded from the study. In this investigation, data from 411 patients with pSjD who were followed at the Department of Internal Medicine, Division of Rheumatology, Erciyes University Faculty of Medicine between January 2013 and June 2024 were retrospectively evaluated. The diagnosis of pSjD was made according to either the 2002 American-European Consensus Group (AECG)(12) classification standards or the 2016 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria(13).Patients diagnosed associated SjD(2) due to coexisting rheumatic diseases, and those exhibiting erosive arthritis on radiographic, were excluded from the study. Those aged under 18 years, individuals with chronic viral hepatitis, and patients with missing data on age at onset or diagnostic parameters were excluded. The onset of pSjD was defined as the moment when illness-specific signs first manifested, including sicca symptoms, arthropathy, parotid enlargement, or, in the case of interstitial lung disease (ILD), symptoms such as cough and dyspnea. Based on age at onset, pSjD patients were classified into three groups: Young-onset SjD (YopSjD, <40 years), Adult-onset SjD (AopSjD,40-60 years), Elderly-onset SjD (EopSjD,>60 years). Borderline patients aged 39 years were included in the YoSJD group, and those aged 61 years were included in the EoSJD group.

Methods

Patients' sicca symptoms, the presence of arthropathy and raynaud phenomenon, hematological parameters erythrocyte sedimentation rate (ESR),

C-reactive protein (CRP), and other laboratory values correspond to those assessed at the time of diagnosis. The presence of ILD, PAH, hepatic involvement, neurological involvement, vasculitis, and malignancy and drugs used in the treatment of SjD was evaluated according to the status at the last follow-up visit. Clinical and laboratory findings, minor salivary gland biopsy results, and diagnostic information of eligible patients were extracted from medical records and the hospital information system. Symptoms associated with pSjD were evaluated at the time of diagnosis and throughout future regular examinations. The Schirmer test assessed ocular dryness, with a result of ≤5 mm/5 minutes deemed positive. Arthropathy was characterized by the occurrence of morning stiffness alongside arthralgia or signs of synovitis. Interstitial lung disease (ILD) was diagnosed with high-resolution computed tomography (HRCT), assessed by two proficient radiologists, and clinically validated by rheumatologists. Morphological alterations observed on HRCT indicative of ILD encompassed reticular abnormalities, ground-glass opacities, nodules, consolidation, cysts, honeycombing, and bronchiectasis in diverse combinations. The ILD subtypes linked to pSjD primarily encompassed nonspecific interstitial pneumonia (NSIP), with typical interstitial pneumonia (UIP), lymphocytic interstitial pneumonia (LIP), and organizing pneumonia (OP).The laboratory assessment encompassed a complete blood count, measurements of complement 3 (C3) and complement 4 (C4) levels, ESR, CRP and and rheumatoid factor (RF) titers. Antinuclear antibodies (ANA) and other autoantibodies were evaluated in the patients; the most frequently detected autoantibodies, including anti-SSA, anti-Ro52, anti-SSB, and anti-centromere protein B (CENPB) antibodies, were analyzed. Leukopenia is characterized by a white blood cell count of less than 4.00 × 10^9/L; neutropenia by a neutrophil count of less than 1.5 × 10^9/L; lymphopenia by a lymphocyte count of less than 1 × 10^9/L; anemia by a hemoglobin concentration of less than 11 g/dL; and thrombocytopenia by a platelet count of less than 100 × 10^9/L. Low C3 and low C4 levels were established as <0.7 g/L and <0.16 g/L, respectively. An elevated ESR was defined as above 20 mm/hour and elevated CRP above 5 mg/l is deemed abnormal. ANA titers were assessed via the indirect immunofluorescence technique on HEp-2 cells, with titers ≥1:100 being positive and titers ≥1:1000 classified as high. Rheumatoid factor (RF) was quantified using an immunoturbidimetric technique, with levels exceeding 14 IU/mL deemed positive.Pulmonary arterial hypertension (PAH) was diagnosed via right heart catheterization by experienced cardiologists using the hemodynamic criteria of mean pulmonary artery pressure (mPAP) >20 mmHg, pulmonary capillary wedge pressure (PCWP) ≤15 mmHg, and pulmonary vascular resistance (PVR) >2 Wood units (WU)(14). Minor salivary gland biopsies were executed by rheumatologists or otolaryngologists, while histological assessments were carried out by pathologists at Erciyes University Faculty of Medicine. A positive biopsy was characterized by localized lymphocytic sialadenitis with a focus score (FOCUS) of ≥1(which implies the presence of more than 50 lymphocytes per 4 mm^2 in the periductal or perivascular space).Neurological involvement was characterized by the existence of notable abnormalities on electromyography (EMG) or central nervous system imaging (CT or MRI) in patients monitored by seasoned neurologists. A diagnosis of malignancy was confirmed in patients using histological analysis, who were thereafter monitored in hematology or oncology outpatient clinics.

Statistical analysis

SPSS version 26.0 was used to conduct statistical analyses (IBM Corp., Armonk, NY, USA). Frequencies and percentages were used to summarize categorical variables. Mean ± standard deviation (SD) was used to represent continuous variables with a normal distribution, while median (interquartile range, IQR) was used to represent those without. The Shapiro-Wilk test was used to determine whether the distribution was normal. When comparing the three groups, normally distributed variables were analyzed using one-way analysis of variance (ANOVA), while non-normally distributed variables were analyzed using the Kruskal–Wallis H test. Categorical variables were compared using the Chi-square test. We used Bonferroni-adjusted post hoc analyses for multiple comparisons. The linear-by-linear association (LLA)

Chi-square test was used to assess trends among the three groups. Statistical significance was defined as a p-value of less than 0.05.

Results

The study comprised 411 pSjD patients in all, ranging in age from 20 to 79. In the entire sample, 93.4% (n = 384) of the patients were female, and the median age was 55 years (interquartile range [IQR]: 47–63). Patients were divided into three groups based on their ages at diagnosis: YopSjD (n = 104), AopSjD (n = 214), and EopSjD (n = 93). In each age category, the percentage of females was 98.1%, 93.9%, and 87.1%, respectively ($p < 0.05$). The proportion of female patients gradually decreased with age, despite the fact that the overall sex distribution was predominately female.The median age at diagnosis was 35.5 years (IQR: 32–38) for the YopSjD group, 50 years (IQR: 45–55) for the AopSjD group, and 65 years (IQR: 62–69) for the EopSjD group ($p < 0.05$). There were also big disparities between the three groups in terms of how long they had the condition. The median disease duration was 60 months (IQR: 36–120) in the YopSjD group and 60 months (IQR: 36–108) in the AopSjD group, but it was much shorter in the EopSjD group at 36 months (IQR: 18–72) ($p < 0.05$) (Table 1).A total of 362 patients (88.08%) tested positive for ANA, with no statistically significant variation between age groups ($p = 0.449$). High-titer ANA (≥1/1000), SSA, SSB, and centromere antibody positivity were observed at comparable frequency across the three age groups ($p > 0.05$). In contrast, RF positive was observed in 27.9% of the YopSjD group 19.2% of the AopSjD group and 35.5% of the EopSjD group ($p = 0.007$).In relation to hypocomplementemia, reduced C3 and C4 levels were more commonly noted in the YopSjD group; however, these differences did not reach statistical significance ($p = 0.288$; $p = 0.301$). An increased erythrocyte sedimentation rate (ESR) was predominantly observed in the EopSjD cohort (46.2%), with a statistically significant variation across age groups ($p < 0.05$). Likewise, heightened CRP levels were predominantly noted in the EopSjD group (37.6%), and this difference was statistically significant

Table 1. Demographic, laboratory, and biopsy characteristics of patients with pSjD at diagnosis.

	Total (n=411)	YopSjD (n=104)	AopSjD (n=214)	EopSjD (n=93)	p value
Age(year)	55 (47-63)	35.5 (29-38.25)[a]	50 (46-55)[b]	65 (61-68)[c]	**<0.05**
Gender(F)(%)	384 (%93.4)	102 (%98.08)[a]	201 (%93.9)[a]	81 (%87.1)[b]	**<0.05**
Disease duration(months)	60 (24-96)	60(36-108) [a]	60 (36-96)[a]	36 (24-72)[b]	**<0.05**
ANA(+)(1/100)(n/%)	362 (%88.08)	95(%91.35)	185 (%86.45)	82 (%88.17)	0.449
ANA positivity (high titer ≥1:1000) (n/%)	208 (%50.61)	57(%54.81)	103 (%48.13)	48 (%51.61)	0.523
Anti-SSA/Ro (n/%)	241 (%58.64)	66 (%63.46)	120 (%56.07)	55 (%59.14)	0.452
Anti-SSB/La (n/%)	67 (%16.30)	22 (%21.15)	32 (%14.95)	13 (%13.98)	0.294
Centromere antibody (n/%)	5 (%1.22)	2 (%1.92)	1 (%0.47)	2 (%2.15)	0.349
RF+(>14 IU/ml)	103 (%25.06)	29 (%27.88)[a a]	41 (%19.16)[a]	33 (%35.48)[a]	**0.007**
Low C3 (n/%)	15 (%3.65)	6 (%5.77)	5 (%2.34)	4 (%4.3)	0.288
Low C4 (n/%)	35 (%8.52)	12 (%11.54)	18 (%8.41)	5 (%5.38)	0.301
Elevated ESR (n/%)	124 (%30.17)	25 (%24.04)[a]	56 (%26.17)[a]	43 (%46.24)[b]	**< 0.05**
Elevated CRP (n/%)	118 (%28.71)	21 (%20.19)[a]	62 (%28.97)[ab]	35 (%37.63)[b]	**0.025**
Focus score ≥1 (n/%)	262 (%63.75)	60 (%57.69)	145 (%67.76)	57 (%61.29)	0.184

a *p* adjusted <0.05 (young-onset pSjD *vs.* adult-onset pSjD) on the basis of *post-hoc* analysis corrected by Bonferroni adjustment. b *p* adjusted <0.05 (adult-onset pSjD *vs.* elderly-onset pSjD) on the basis of *post-hoc* analysis corrected by Bonferroni adjustment. c *p* adjusted <0.05 (young-onset pSjD *vs.* elderly-onset pSjD) on the basis of *post-hoc* analysis corrected by Bonferroni adjustment.

(p = 0.025). A focus score ≥1 was detected in 63.75% of the patients. The distribution by age group was 57.69%, 67.76%, and 61.29%, respectively. There was no statistically significant difference in focus scores among the age groups (p = 0.184) (Table 1).

Upon evaluation of clinical data, the predominant complaints identified were dry eyes (81.3%) and dry mouth (66.7%). The prevalence of dry eyes was 75.0% in the YopSjD group, 84.6% in the AopSjD group and 80.6% in the EopSjD group, with no statistically significant difference observed among the groups (p = 0.119). Dry mouth was noted in 66.3%, 64.5%, and 72.0% of the YopSjD, AopSjD, and EopSjD groups, respectively, with this distribution not achieving statistical significance (p = 0.460).Arthropathy was detected in 71% of the entire patient population. The prevalence, when analyzed by age group, was 76% in the YopSjD group, 64.5% in the AopSjD group, and 80.6% in the EopSjD group, demonstrating a statistically significant difference among the groups (p = 0.007). Raynaud's phenomenon was identified in 3.59% of patients, with no statistically significant variation across age groups (p = 0.608).The most commonly seen hematological abnormality was lymphocytopenia (18.98%), with no significant variation among age groups (p = 0.274). Anemia was more common in the EopSjD group (20.43%), and this difference was statistically significant (p = 0.040). No substantial difference was seen among the groups concerning leukopenia (p = 0.149). Despite a tendency for the neutrophil-to-lymphocyte ratio to rise with age (median values: YopSjD = 1.96, AopSjD = 1.88, EopSjD = 2.18), this variation did not achieve statistical significance (p = 0.107).In assessing patients for systemic involvement, the incidence of pulmonary arterial hypertension (PAH) was identified in a total of 15 individuals. According to the World Health Organization (WHO) classification, 6 patients (40.0%) had Group 1 PAH, 4 patients (26.7%) had Group 2 PAH, 4 patients (26.7%) had Group 3 PAH, and 1 patient (6.6%) had Group 4 PAH. PAH was markedly elevated in the elderly-onset group (EopSjD: 8.60%; p < 0.05). Nonetheless, upon eliminating patients with chronic diseases that potentially affect the onset of PAH (ischemic heart disease, asthma, chronic obstructive pulmonary disease, heart failure, and interstitial lung disease), the EopSjD group still had the greatest prevalence of PAH at 3.8%. However, this difference was no longer statistically significant (p = 0.225).Interstitial lung disease (ILD) was present in 11.96% of patients. Among the 50 patients diagnosed with ILD, 38 had an NSIP pattern, 10 had a UIP pattern, and 2 had a LIP pattern. ILD was significantly more frequent in the EopSjD group (25.81%; p < 0.05). In addition, 9 of the 27 male patients (33.3%) were in the EopSjD group with ILD.Of the 12 patients with liver involvement, 9 were diagnosed with autoimmune hepatitis and 3 with primary sclerosing cholangitis. Among vasculitic manifestations, the most common type was cutaneous leukocytoclastic vasculitis (n = 8). Although solid tumors were the most frequent malignancies overall, subgroup analysis revealed that lymphoma was the most common type (n = 7). Among solid malignancies, breast cancer was the most frequent diagnosis, observed in 6 patients. No statistically significant differences were found among the age groups regarding other systemic manifestations, including liver involvement, neurological involvement, vasculitis, and malignancy (Table 2).

An assessment of the pharmacological treatments for pSjD indicated that hydroxychloroquine was the most commonly administered medication, with 86.61% of patients undergoing this therapy. In the comparison of the three subgroups, Hydroxychloroquine usage was 84.6% in the YopSjD group, 90.7% in the AopSjD group, and 79.6% in the EopSjD group, indicating a statistically significant difference (p = 0.025), with the AopSjD group exhibiting the highest utilization. Glucocorticoids were administered to 26.2% of patients overall, with a much greater incidence in the EopSjD group relative to the others (YopSjD: 23.1%; AopSjD: 22.4%; EopSjD: 38.7%) (p = 0.008). Azathioprine was administered to 6% of all patients, rising to 11.8% in the EopSjD group, with this disparity being statistically significant (p = 0.030) (Figure-1). Conversely, no statistically significant differences were seen among the groups regarding the utilization of conventional synthetic disease-modifying antirheumatic medications (csDMARDs) or rituximab (p = 0.52 and p = 0.94, respectively). The utilization of mycophenolate mofetil (MMF) in the EopSjD group was 5.4%, surpassing that of the other groups; however, the difference was not statistically significant (p = 0.27) (Table 3).

Table 2. Clinical characteristics of patients with pSjD at diagnosis.

	Total (n = 411)	YopSjD (n=104)	AopSjD (n=214)	EopSjD (n=93)	p value
Dry eye	334 (%81.3)	78 (%75)	181 (%84.6)	75 (%80.6)	0.119
Dry mouth	274 (%66.7)	69 (%66.3)	138 (%64.5)	67 (%72.0)	0.460
Arthropathy	292 (%71)	79 (%76)[a a]	138 (%64.5)[a]	75 (%80.6)[a]	**0.007**
Raynaud's phenomenon	15 (%3.59)	5 (%4.81)	8 (%3.74)	2 (%2.15)	0.608
Anemia	59 (%14.36)	18 (%17.31)[a a]	22 (%10.28)[a]	19 (%20.43)[a]	**0.040**
Leukopenia	76 (%18.49)	14 (%13.46)	47 (%21.96)	15 (%16.13)	0.149
Lymphocytopenia	78 (%18.98)	18 (%17.31)	37 (%17.29)	23 (%24.73)	0.274
Neutrophil-to-lymphocyte ratio	1.98 (1.44-2.51)	1.96 (1.46-2.37)	1.88 (1.40-2.47)	2.18(1.51 - 2.76)	0.107
Liver involvement	12 (%2.87)	3 (%2.88)	7 (%3.27)	2 (%2.15)	0.866
Neurological involvement	16 (%3,89)	4 (%3,84)	10 (%4.67)	2 (%2.15)	0.532
Peripheral nervous system	7 (%1.71)	1 (%0.09)	4 (%1.86)	2 (%2.15)	0.576
Central nervous system	9 (%2.18)	3 (%2.88)	6 (%2.8)	0 (%0)	0.260
PAH	15 (%3,64)	0 (%0)[a]	7 (%3.27)[a a]	8 (%8.60)[a]	< **0.05**
Isolated PAH	6 (%1.4)	0 (%0)	4(%2.2)	2 (%3.8)	0.225
Interstitial lung disease	50 (%11.96)	4 (%3.85)[a]	22 (%10.28)[a]	24 (%25.81)[a]	< **0.05**
Vasculitis	10 (%2.4)	1 (%0,96)	4 (%1.9)	5 (%5.4)	0.081
Malignancy	26 (%6,29)	3 (%2.88)	16 (%7.48)	7 (%7.53)	0.249
Solid malignancy	17 (%4.1)	1 (%0,96)	12 (%5.6)	4 (%4.3)	0.148
Hematological malignancy	9 (%2,19)	2 (%1.92)	4 (%1.87)	3 (%3.23)	0.740
Lymphoma	7(%1,7)	2 (%1.92)	2(%0,9)	3 (%3.23)	0,35

a *p* adjusted <0.05 (young-onset pSjD *vs.* adult-onset pSjD) on the basis of *post-hoc* analysis corrected by Bonferroni adjustment. b *p* adjusted <0.05 (adult-onset pSjD *vs.* elderly-onset pSjD) on the basis of *post-hoc* analysis corrected by Bonferroni adjustment.

Discussion

While pSjD is frequently observed in middle-aged women, recent research has increasingly acknowledged that its clinical features may differ based on the age of initiation(8-10). Our work illustrates that the age at which the disease begins significantly affects the clinical symptoms of pSjD, with varying age groups displaying unique clinical and immunological characteristics. The median ages in our study were 35.5 years for the YopSjD group, 50 years for the AopSjD group, and 65 years for the EopSjD group ($p < 0.05$). The sex distribution revealed that women constituted 93.43% of our entire cohort, aligning with the established female predominance in pSjD(4, 5). In the EopSjD group, the percentage of women diminished to 87.1%, signifying a relative rise in the proportion of men as age at diagnosis increased. Potential contributing variables to this trend may encompass the impact of aging on autoimmunity, genetic and hormonal disparities, and sex-related variations in healthcare-seeking behavior(15).The observation that the median disease duration in the EopSjD group was considerably shorter (36 months) than in the other groups (60 months in both the YopSjD and AopSjD groups) ($p < 0.05$) is important. This may pertain to the notion that managing symptoms that manifest in later life can be more challenging to endure than those that arise earlier. Consequently, EopSjD patients, who may experience an intensified urgency to pursue medical care due to their symptoms, can exhibit a reduced disease duration(9).Our study's serological findings revealed a significant outcome that contradicts the prevailing consensus in the literature. Although it is commonly noted that autoantibodies like anti-SSA, anti-SSB, and rheumatoid factor (RF) are more prevalent in

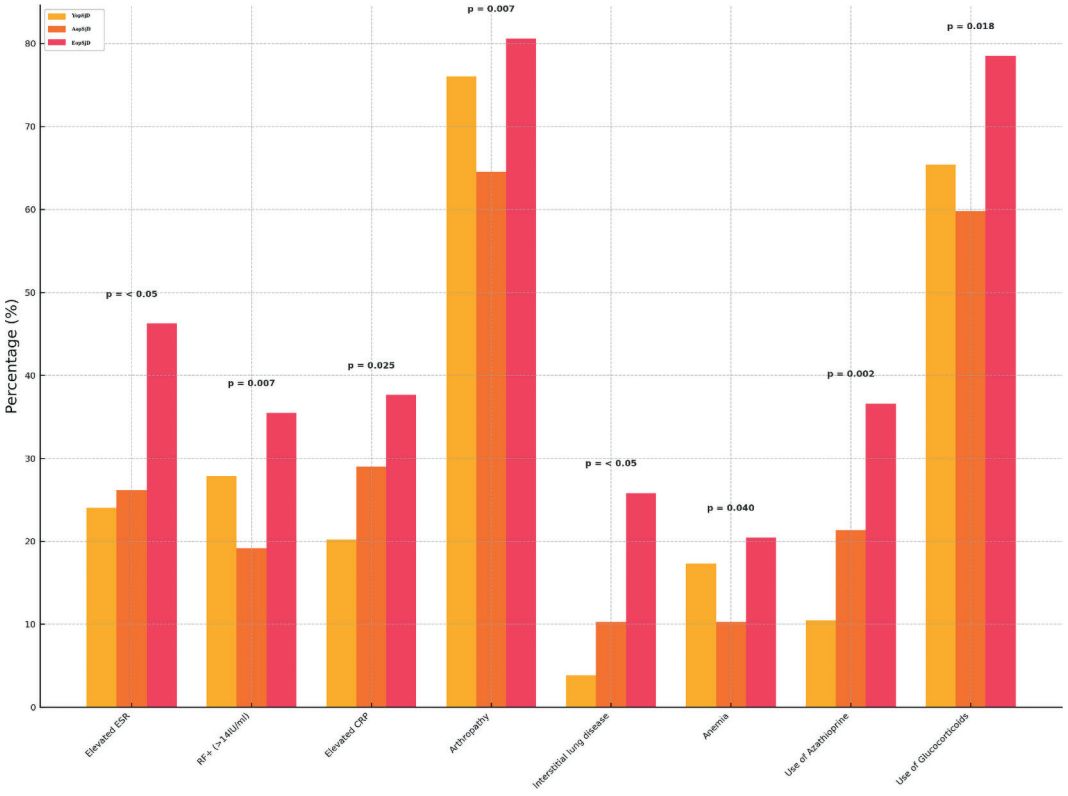

Figure 1. Statistically significant findings in EopSjD patients. *Abbreviations:* ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor.

Table 3. Immunosuppressive medications used by patients.

	Total (n=411)	YopSjD (n=104)	AopSjD (n=214)	EopSjD (n=93)	p value
Hydroxychloroquine	356 (%86,61)	88 (%84.6)[ab]	194 (%90.7)[a]	74 (%79.6)[b]	**0.025**
CsDMARDs*	29 (%7,1)	7 (%6,7)	13 (%6,1)	9 (%9,7)	0,52
Glucocorticoids	108 (%26.2)	24 (%23,1)[a]	48 (%22,4)[a]	36 (%38,7)[b]	**0,008**
Azathioprine	25 (%6)	5 (%4,8)[ab]	9 (%4,2)[a]	11 (%11,8)[b]	**0,030**
Mycophenolate mofetil	12 (%2.9)	2(%1,9)	5 (%2,3)	5 (%5.4)	0,27
Rituximab	5 (%1.2)	1 (%0.9)	3 (%1,4)	1 (%1)	0,94

*conventional synthetic disease-modifying anti-rheumatic drug. a *p* adjusted <0.05 (young-onset pSjD *vs.* adult-onset pSjD) on the basis of *post-hoc* analysis corrected by Bonferroni adjustment. b *p* adjusted <0.05 (adult-onset pSjD *vs.* elderly-onset pSjD) on the basis of *post-hoc* analysis corrected by Bonferroni adjustment.

younger-onset patients(9, 11, 16), our cohort revealed a significantly greater RF positivity in the EopSjD group (35.48%) (p = 0.007). This rate was much greater than those recorded in the YopSjD group (27.88%) and the AopSjD group (19.16%). The prevalence of anti-SSA and anti-SSB positivity was comparable among the groups (p = 0.452 and p = 0.294, respectively). A 2022 cohort research conducted by Luo et al. in China demonstrated that the positivity of anti-SSA, anti-SSB, and RF substantially declines with age(9). Retamozo et al. similarly showed that the positive of anti-Ro, anti-La, and RF decreased with advancing age at diagnosis(10). The observed difference in our study may be due to the genetic and ethnic traits of our study population. The elevated RF positive in the EopSjD group may be associated with the increased

prevalence of arthropathy within this subgroup. It should also be noted that low-titer RF positivity may occur in elderly individuals due to age-related immune activation or infections, which could partly explain the higher RF positivity observed in the elderly-onset group(17). The prevalence of raised erythrocyte sedimentation rate (ESR) as an inflammatory marker was considerably greater in the EopSjD group (46.24%) than in the other groups (YopSjD: 24.04%; AopSjD: 26.17%) ($p < 0.05$). Likewise, increased CRP levels were considerably more prevalent in the EopSjD group (37.63%) ($p = 0.025$), reinforcing the hypothesis that late-onset pSjD may manifest against a more prominent inflammatory backdrop(18). The findings indicate that the heightened burden of chronic inflammation associated with aging may contribute to the etiology of pSjD. Complement levels (C3 and C4) exhibited no significant differences across the groups ($p = 0.288$ and $p = 0.301$, respectively). ANA positivity (88.08%) and high-titer ANA positivity (50.61%) had a comparable distribution across age groups ($p = 0.449$ and $p = 0.523$, respectively). These results align with other studies(19, 20). Similarly, the proportion of patients with a focus score ≥1 did not exhibit significant differences among the groups (63.75%; $p = 0.184$), indicating that glandular inflammation does not substantially vary in late-onset pSjD. Although there are studies in the literature reporting that the focus score is lower in elderly patients due to age-related fibrosis or atrophy(8, 18), there are also studies with similar focus scores, as in our study (15).Interstitial lung disease (ILD) is the predominant pulmonary consequence of pSjD and constitutes a significant source of morbidity and mortality(21, 22). The research of the Sjögren Big Data Consortium, encompassing 12,753 patients, revealed that each additional year in age at diagnosis elevates the probability of pulmonary involvement by 0.22%(10). In the study conducted by Luo et al., the incidence of ILD exhibited a linear increase with age and was markedly elevated in the EopSjD group (48.1%) compared to the YopSjD group (14.3%)(9). The prevalence of ILD in the EopSjD group was 25.81%, greatly surpassing that of the other groups ($p < 0.05$). This discovery reinforces the idea that late-onset pSjD could be a significant risk factor for pulmonary involvement. Age-associated alterations in the immune system and extended exposure to environmental variables may augment this heightened risk(23-25).Additionally, it is significant that ILD was identified in 15 of the 27 male patients with pSjD. Among them, 9 (60%) were allocated to the EopSjD group, while the remaining 6 were assigned to the AopSjD group. The prevalence of ILD was 9.11% in female patients and 55.56% in male patients. The occurrence of ILD was markedly more prevalent in males ($p < 0.05$). Comparable findings have been documented in the literature, indicating that male sex constitutes a risk factor for ILD(26, 27).The prevalence of arthropathy was greater in the EopSjD group (80.6%) and the YopSjD group (76.0%) than in the AopSjD group (64.5%). This data indicates that pSjD with onset in either advanced or younger age may have more significant joint involvement compared to onset around middle age. Our investigation revealed a statistically significant difference between the AopSjD and EopSjD groups in this context ($p = 0.007$). The results may be linked to the intensified inflammatory process associated with pSjD compounded by aging, thereby elevating the incidence of joint involvement. Moreover, the increased incidence of degenerative joint illnesses, such as osteoarthritis, in elderly persons may exacerbate pSjD-related arthropathy. The elevated prevalence of RF positive noted in the EopSjD group (35.48%) may also account for the heightened incidence of arthropathy within this subgroup. While RF positive is often linked to rheumatoid arthritis, it is also seen as an indicator of joint involvement in patients with pSjD(28).No statistically significant differences were seen between the groups concerning sicca symptoms which are the primary indications of glandular involvement ($p = 0.119$; $p = 0.460$). Despite the prevalence of xerostomia reaching 72% in the EopSjD group, this difference did not achieve statistical significance. Consistent with our findings, several studies in the literature have also indicated no significant differences among patient groups diagnosed at an earlier stage of the disease(4).The EopSjD group exhibited a considerably greater prevalence of anemia (20.43%) compared to the other groups in terms of hematological results. This may pertain to issues such as age-related escalations in anemia of chronic disease or nutritional inadequacies. It is also

well recognized that pSjD can induce anemia as a consequence of persistent inflammation(29). No notable changes were detected between the groups for lymphocytopenia or leukopenia, aligning with prior literature reports(4, 15). The neutrophil-to-lymphocyte ratio (NLR), acknowledged as a marker of systemic inflammation(30), had a tendency to rise with age in our sample, although this trend did not achieve statistical significance. This observation may indicate a more pronounced baseline inflammatory condition in the EopSjD group. Moreover, the heightened ESR and CRP levels found in this cohort corroborate this conclusion. In patients with primary Sjögren's disease the probability of getting lymphoma is 10 to 44 times greater than in healthy individuals. Marginal zone lymphoma, diffuse large B-cell lymphoma, and mucosa-associated lymphoid tissue (MALT) lymphoma comprise over 90% of these instances. Moreover, patients with pSjD exhibit a greater prevalence of solid malignancies, including lung, breast, and thyroid cancers, in addition to non-melanoma skin cancers, relative to the general population(31). In our study, 6.29% of patients with pSjD were diagnosed with malignancy, with a solid malignancy rate of 4.1%. No statistically significant differences were detected between the groups regarding malignancy or lymphoma ($p = 0.249$; $p = 0.35$). The heightened risk of lymphoma in pSjD is well established; nevertheless, numerous investigations have also indicated a greater incidence of solid tumors in this demographic(31, 32). Consequently, meticulous monitoring of pSjD patients is essential not only for hematological malignancies but also for solid tumors.Neurological involvement is an important extraglandular manifestation of pSjD and can affect both the peripheral and central nervous systems(33). In our study, the overall prevalence of neurological involvement was 3.89%, with no statistically significant differences observed between age groups ($p = 0.532$). This rate is generally consistent with the prevalence range of 2–20% reported in large series in the literature(34). In a meta-analysis by Retamozo et al., the frequency of peripheral nervous system involvement increased with age; however, no distinct pattern differences were observed in the distribution of neurological subtypes(10).In our study, the higher use of glucocorticoids, azathioprine, and MMF in older patients may be related to a greater need for immunosuppressive agents to maintain clinical remission in this group. Furthermore, the preference for these agents in the management of more frequently observed manifestations such as arthropathy and interstitial lung disease (ILD) in the EopSjD group may also contribute to this finding. However, it is well known that immunosuppressants such as azathioprine, which are more commonly used in the EopSjD group, may increase the long-term risk of malignancy(35-37). Therefore, older patients receiving immunosuppressive therapy should be closely monitored for the development of malignancies.Hydroxychloroquine use was found to be highest in the AopSjD group, and this difference was statistically significant ($p = 0.025$). The high prevalence of hydroxychloroquine use among pSjD patients (86.61%) may be attributed to its preference in the management of more "classical" pSjD manifestations, such as joint and cutaneous involvement(38). In contrast, the lower rate of use in the EopSjD group may be related to concerns regarding potential ocular and cardiac adverse effects associated with hydroxychloroquine therapy.Our study has several limitations. Its retrospective design and single-center nature may limit the generalizability of the findings. Additionally, the lack of long-term follow-up data restricted our ability to evaluate disease progression and treatment outcomes across different age groups. Furthermore, potential confounding factors such as comorbidities and polypharmacy in older patients were not fully accounted for, which may have influenced certain clinical associations. In our study, antisynthetase antibodies were not routinely assessed in anti-Ro52–positive patients; this was considered one of the limitations of the study. Another limitation of our study is the lack of longitudinal follow-up data to evaluate temporal changes in clinical manifestations. Because of its retrospective and cross-sectional design, we were unable to assess potential phenotypic transitions of patients between age-onset groups. Future prospective, long-term studies are warranted to clarify the natural course and phenotypic evolution of primary Sjögren's disease across different age groups. These limitations highlight the need for larger, multicenter, prospective studies involving more diverse patient populations and longer observation periods to validate and expand upon our findings.

Conclusion

This study evaluated the impact of age at onset on the clinical and serological phenotype of pSjD in a Turkish population. Our findings confirm that pSjD exhibits distinct phenotypic variations according to age at onset. EopSjD is characterized by a higher prevalence of interstitial lung disease, more frequent anemia, RF positivity, and arthropathy. These patients require immunosuppressive therapy at rates comparable to other age groups; however, the increased use of agents such as azathioprine and corticosteroids-drugs that require more cautious administration in older adults—is noteworthy. In elderly patients diagnosed with pSjD, proactive screening and close monitoring for ILD may play a critical role in reducing disease-related morbidity and mortality. Further multicenter, prospective studies are needed to better elucidate the heterogeneous nature of pSjD and to inform the development of age-specific therapeutic targets.

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Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

Declaration on the Use of AI: The authors declare that no generative AI tools were used in the writing, editing, or preparation of this manuscript.

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