Differences in clinical phenotypes of primary Sjögren's syndrome depending on early or late onset

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Abstract

Background. Previous research suggests that systemic involvement in primary Sjögren's syndrome (pSS) is a marker of disease prognosis.

Objectives. To evaluate pSS disease activity and the clinical phenotype of pSS patients depending on the age at diagnosis with long-term follow-up.

Materials and methods. The study group consisted of patients diagnosed with pSS based on the 2016 pSS classification criteria.

Results. The study group consisted of 46 patients with early-onset pSS (≤35 years of age) and 32 patients with late-onset pSS (≥65 years of age). The study group was identified from a total of 228 patients diagnosed with pSS. There were no differences regarding the frequency of eye and mouth dryness, focus score (FS) ≥1 or anti-SSA/SSB antibodies depending on age. Rheumatoid factor (RF) was more common among older patients ($p > 0.05$). In the overall assessment of disease activity using European League Against Rheumatism (EULAR) Sjögren Syndrome Disease Activity Index (ESSDAI), no differences related to age were observed on the first and last visit (after 36 months on average). Lymphadenopathy and changes in the hematology domain ($p < 0.05$) were more common in patients with the early-onset phenotype. Changes in the lungs and musculoskeletal system occurred regardless of age.

Conclusions. Patients with early-onset pSS differ from those with late-onset pSS in terms of higher incidence of peripheral lymphadenopathy and cytopenia. The involvement of lung tissue and joints as well as dryness symptoms are common in pSS regardless of age. The RF plays a role in the pathomechanism of pSS development.

Key words: disease activity, age, Sjögren's syndrome, antinuclear antibodies

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Background

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by inflammation of the salivary and lacrimal glands, causing a reduction in exocrine secretion that ultimately leads to clinical presentation of sicca symptoms.[1] Aside from sicca syndrome, a typical symptom is chronic fatigue. The pSS is a heterogeneous disease that, in addition to dryness, presents with involvement of multiple organs and systems (extraglandular manifestations).

Systemic involvement corresponds to disease prognosis.[2] The incidence of pSS is estimated at 61 per 100,000 people in the general population, with the highest prevalence encountered in Europe.[3] Differences regarding the prevalence and incidence of pSS are thought to be due to variation in study design and classification criteria.[3] The disease overwhelmingly affects middle-aged women. The mean age at the time of pSS diagnosis is 56 years, with another peak occurring between 20 and 40 years.[4] Several factors, including age, appear to determine the various clinical phenotypes of pSS.[5] To date, little data have been published regarding the relationship between age and clinical signs of pSS. As a result, the current research findings are divergent and inconclusive. In systemic lupus erythematosus and rheumatoid arthritis, most studies agree that late onset of the disease is associated with involvement of fewer organs and better prognosis.[6,7] However, in the case of pSS, published data on the topic are scarce. Previous studies suggest differences in clinical and immunologic phenotypes between patients with early and late onset of the disease. Furthermore, the risk of developing lymphoma as a complication of pSS seems to be age-dependent, according to some authors.[8] An advanced age at diagnosis is also regarded as a risk factor for increased mortality, along with, for example, male sex, parotid enlargement, extraglandular involvement, and some immunologic abnormalities.[9,10] In particular, age seems to be an important factor in the clinical phenotype of pSS.[2,11] Brito-Zerón et al. suggested that the systemic phenotype of pSS is strongly influenced by personal determinants, such as age, gender, ethnicity, and place of residence, which are key geoepidemiological players driving the expression of systemic disease at diagnosis.[12]

Clinical variability in pSS can hinder both, early diagnosis and personalization, and selection of appropriate treatment. This is especially important in the early and late phenotype of the disease to accelerate the correct diagnosis while still in its early stages. To date, few papers and clinical observations on this issue in pSS have been published. In addition, there are few analyses available in the literature on the subsequent course of pSS in patients with early and late onset of the disease.

Objectives

This study aimed to assess the activity and clinical phenotype of pSS according to the age of disease onset (early- compared to late-onset phenotypes) and assess the activity of the disease over long-term follow-up.

Materials and methods

Patient selection

A total of 228 patients over 18 years of age who were diagnosed with pSS in our department from 2009 to 2020 based on the 2016 pSS classification criteria, were considered eligible for this study.[13] Patients with an additional systemic connective tissue disease, especially systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), were excluded. The selected study group consisted of 46 patients with early-onset pSS (≤35 years of age at the time of diagnosis and 32 patients with late-onset pSS (≥65 years of age at the time of diagnosis).

Assessment of disease activity and follow-up

Patients underwent routine labial salivary gland biopsy (LSGB) under local anesthesia with 10% lidocaine solution for histopathological assessment of characteristic lymphocytic infiltrates typical of pSS following the current guidelines[14] (focal lymphocytic sialadenitis and focus score ≥1 foci/4 mm^2). Disease activity was assessed in all patients using the European League Against Rheumatism (EULAR) Sjögren Syndrome Disease Activity Index (ESSDAI).[15] Laboratory tests were performed following current guidelines for the diagnosis and assessment of pSS activity, including assessment of the presence of rheumatoid factor (rheumatoid factor (RF), nephelometric method), antinuclear antibodies (ANA and immunofluorescence (IF) method), antibodies to extractable nuclear antigens (extractable nuclear antigen (ENA), enzyme-linked immunosorbent assay (ELISA)), C3 and C4 components of the complement system, and evaluation of immunoglobulin concentrations. Assessment of disease activity was carried out at least twice: at the time of the diagnosis of pSS and during the last follow-up visit (at least 6 months after the 1st visit). The average follow-up duration was 36 months.

This study was approved by the ethics committee of the Wroclaw Medical University, Wrocław, Poland (decision No. 836/2020) and was conducted in compliance with the Declaration of Helsinki. Written informed consent to participation in this study was obtained from all patients.

Statistical analysis

Statistical analysis was performed using STATISTICA v. 10 software package (StatSoft Inc., Tulsa, USA). The Mann–Whitney U test was used to compare the distributions of quantitative variables in 2 independent groups, i.e., to compare the ESSDAI point values and age between the early- and late-onset groups. The χ^2 test was used to assess relationships between dichotomous variables. Statistical significance was considered at $p \leq 0.05$.

Results

Among the 228 patients diagnosed with pSS, 20% (n = 46) had early-onset disease (≤35 years of age at the time of diagnosis and 14% (n = 32) had late-onset disease (≥65 years of age at the time of diagnosis). The majority of patients were diagnosed with pSS after the age of 35 but before the age of 65 (66% of patients (n = 150)). Symptoms of eye and mouth dryness were observed in 93% (n = 43) and 85% (n = 39) of patients with early-onset pSS and 96% (n = 31) and 100% (n = 32) of patients with late-onset pSS, respectively (the differences were not statistically significant; see Table 1). Salivary gland biopsy was not performed in 2 patients from each subgroup due to a lack of consent (4 patients in total). Focus score (FS) ≥1 was found in 90% (n = 27) of patients with late-onset pSS and 82% (n = 36) of patients with early-onset pSS. Specific anti-SSA antibodies were more common in patients with early-onset (89%, n = 41) than with late-onset pSS (72%, n = 23), but this difference was not statistically significant. Anti-SSB antibodies were found in a similar proportion of patients in each subgroup. The RF was more common among older patients (72% compared to 67%; p = 0.86). The C3 hypocomplementemia was found in approx. 15% of patients in each subgroup, while a reduced C4 serum concentration was more often observed among patients over the age of 64 (p = 0.28). In the global assessment of disease activity using ESSDAI, there was a higher pSS activity among younger patients (on average, 7.8 compared to 6.0 points; p = 0.11; Table 2). For the individual ESSDAI domains, the 2 subgroups differed with regard to lymphadenopathy and hematological domains, with organ involvement significantly more common among patients under the age of 36.

Table 1. Characteristic of patients with pSS depending on age at the time of diagnosis

Parameters	Patient age ≤35 years	Patient age ≥65 years	p-value
Number of patients	46	32	–
Age at time of pSS diagnosis SD	29 (min 17; max 35) 5.3	70 (min 65; max 85) 5.0	–
Mean age at the last visit (SD)	32 (5.2)	74 (5.5)	–
Positive ocular symptoms n % of patients	 43 93	 31 96	1.0
Positive oral symptoms n % of patients	 39 85	 32 100	0.62
Positive Schirmer test n % of patients	 40 87	 31 96	0.86
Focus score ≥1 n % of patients	N/A 2 36 82	N/A 2 27 90	0.86
Positive anti-SSA ab n % of patients	 41 89	 23 72	0.6
Positive anti-SSB ab n %	 30 65	 20 62	1.0
Positive RF (nv 0–14 IU/mL) n % of patients	 31 67	 23 72	0.86
Low C3 (nv 0.9–1.8 g/L) n %	N/A 1 7 15	 5 16	1.0
Low C4 (nv 0.1–0.4 g/L) n % of patients	N/A 1 3 7	 5 16	0.28

pSS – primary Sjögren's syndrome; n – number of patients; ab – antibodies; RF – rheumatoid factor; nv – normal value.

Table 2. Evaluation of pSS activity depending on a patient's age at the time of diagnosis

Parameters	Patient's age ≤35 years	Patient's age ≥65 years	p-value	z-score
ESSDAI score at the time of pSS diagnosis	7 (median) 9 (IQR)	5 (median) 5 (IQR)	0.11	1.48
ESSDAI domains (n/% of patients, max value-points in the domain): constitutional lymphadenopathy glandular articular cutaneous pulmonary renal muscular peripheral nervous system central nervous system hematological biological	 7/15 (max 6) 10/22 (max 4) 19/41 (max 4) 22/48 (max 4) 5/11 (max 9) 7/15 (max 10) 2/4 (max 5) 0 0 0 27/59 29/63	 1/3 (max 3) 1/3 (max 8) 9/28 (max 4) 18/56 (max 4) 5/16 (max 6) 9/28 (max 15) 0 0 1/3 (max 10) 0 6/19 16/50	 0.14 <0.05 0.49 0.69 0.73 0.28 0.51 0.41 <0.03 0.57	–
New ESSDAI onset during the observation period [n/% of patients]	8/17	10/31	0.29	–
Lymphoma MGUS	0 0	0 2		–

pSS – primary Sjögren's syndrome; ESSDAI – European League Against Rheumatism (EULAR) Sjögren Syndrome Disease Activity Index n – number of patients; MGUS – monoclonal gammopathy of undetermined significance; IQR – interquartile range.

Discussion

Our findings show that in 2/3 of pSS patients, the disease manifests between the age of 36 and 64. Only in 1/3 of cases did the disease begin at a very young age (≤35 years) or at an older age (≥65 years), which is in line with previous observations.[16] However, since pSS is one of the most common diseases in rheumatology, this represents a relatively large group of patients.[17] The early-onset pSS phenotype dominates this population of patients. The age of disease onset may be relevant for the clinical course and prognosis. Patients with the early-onset phenotype were significantly more likely to have lymphadenopathy and hematological disorders (most often lymphopenia and neutropenia, data not presented), although we did not observe any significant differences in serological abnormalities between early- and late-onset groups. We also observed disease deterioration during long-term follow-up of the late-onset group, despite higher baseline disease activity in early-onset patients (in both cases, the differences were nonsignificant).

The pSS is associated with several immunological abnormalities, of which positive ANA results are the most frequently detected. Anti-SSA antibodies are the most specific abnormality, while cryoglobulins and hypocomplementemia are the main prognostic markers.[18] Our analysis showed that anti-SSA antibodies are present regardless of age, as is hypocomplementemia. Observations made by Chinese researchers indicated that patients with early-onset pSS were more likely to have reduced complement C3 levels,[19] which was not confirmed by our study of a Caucasian population. However, our observations do confirm previous reports of a higher incidence of hematological disorders among younger patients, even though the studies involved different ethnic groups (Asians compared to Caucasians). Direct involvement of antibodies against muscarinic type 3 receptors located on leukocytes has been implicated in the pathomechanism of leucopenia during the course of pSS.[20] To date, anti-acetylcholine type 3 receptor (M3R) antibodies have been shown to be more common in younger patients and patients with hyperglobulinemia.[21]

According to the previous research, patients with the early-onset phenotype of pSS have a higher incidence of lymphadenopathy, RF and anti-SSA antibodies.[8,22] Although Tishler et al. reported more frequent organ involvement in the form of parotid gland enlargement, joint involvement and central nervous system involvement in patients with early-onset pSS, these results were not statistically significant.[5] In our patient sample, lymphadenopathy was more common in young patients. However, we did not observe any difference in the frequency of RF and anti-SSA antibodies. Admittedly, RF was recorded slightly more often in elderly patients, but the differences were statistically insignificant.

The RF is a key marker of pSS and is found in the majority of patients. As the likelihood of finding RF in a significant titer increases with age,[23] we expected to observe it more frequently in the older subgroup in our analysis. Indeed, the prevalence of RF in older patients (≥65 years) was higher than in patients with early disease onset (72% compared to 67%), although these differences were not statistically significant. The similar prevalence of RF in pSS patients irrespective of age may prove the involvement of RF in the pathogenesis and development of pSS. Determination of RF titers may play a central role in differentiating pSS from non-autoimmune causes of sicca syndrome. However, they are not included in the current pSS classification criteria[13] despite the attempts in 2012 to include RF among the primary criteria domains.[24] Furthermore, it is thought that the presence of RF in pSS patients may be linked to increased disease activity and lymphoma,[25] especially when considered in combination with other recognized risk factors for developing lymphoproliferative complications, such as an older age, enlargement of the salivary glands, reduced C4 component of the complement system, and the presence of cryoglobulins, leukopenia or monoclonal gammopathy. In our analysis, no patients were diagnosed with lymphoma. By contrast, in another published study, lymphomas were seen more commonly in older patients.[16]

Ramos-Casals et al. reported that adult pSS patients with early disease onset at the age of 35 had a higher frequency of autoantibodies and incidence of lymphomas than patients with late disease onset. They concluded that age at disease onset was of prognostic value,[8] which we did not confirm in any way in the present study. The likely insufficient (too small) study population is one potential explanation, and further studies are needed to confirm this hypothesis. Recent data also suggest that the risk of developing lymphoma depends on different predisposing factors in relation to the age of the onset of the disease, and that the distribution of lymphoma is different across time among early- and late-onset patient populations.[16] In our observations, among patients ≥65 years, only monoclonal gammopathy of undetermined significance (MGUS) was observed in 2 patients, which might relate to pSS activity or a patient's age (higher risk of MGUS in this age group). About 3% of people over the age of 50 and 5% of people aged 70 and older have M protein in their blood; the highest incidence is among adults aged 85 and older.[26,27]

The ESSDAI questionnaire is used to assess organ damage in pSS. It consists of 12 domains addressing the most important – although not all – clinical manifestations of pSS. The guidelines developed by Seror et al. specify the exact duration and detailed definitions assigned to each individual symptom.[15] In the present study, we assessed disease activity using ESSDAI at the time of diagnosis and subsequent visits. On average, the last visit took place 36 months after the diagnosis of pSS in both subgroups.

All patients were treated according to locally and globally accepted pSS treatment guidelines, depending on their symptoms and organ involvement. It is particularly

noteworthy that, in patients with the late phenotype, we were more likely to observe disease deterioration over long-term follow-up reflected by an increase in ESSDAI, although this change was not statistically significant. These findings contrast with recently published observations where a diagnosis of pSS at a younger age was associated with a poorer prognosis of the disease course.[28] Similar to a multicenter study involving a large group of patients,[12] in our patient population, higher ESSDAI was identified in patients with early-onset compared to late-onset pSS (7.8 compared to 6.0) at baseline, but statistically significant differences were ultimately not demonstrated.

Deviations in blood count and lymphadenopathy are observed more often in younger pSS patients. According to some authors, lymphadenopathy in young patients, as compared to the older patients, is an independent factor for the development of lymphoma in pSS.[16] Generally, identification of lymphadenopathy may allow earlier pSS diagnosis in these patients, for whom the diagnosis may be complicated because of the less pronounced expression of sicca features.[24] In our observations, more than half of patients ≤35 years of age (85%) reported symptoms of dry eyes and mouth, but this rate of dryness was still lower than in older patients (100%).

In most publications to date, lung lesions are typical for patients with late-onset pSS.[16,25] However, the data are still inconclusive.[16,22] According to Zhao et al., patients with pSS pulmonary involvement are more likely to have enlarged major salivary glands.[19] In our group of patients, lung lesions coexisted with enlargement of major salivary glands. The prevalence of organ involvement in both locations was independent of age, similarly to lymphocytic infiltrations in LSGB corresponding to pSS.[14] As demonstrated by Kakugawa et al., LSGB and FS results correlate with the presence and activity of lung lesions.[29] The authors showed that higher FS values were observed mainly in pSS patients with respiratory tract involvement. Furthermore, in our patient group, we more often observed FS ≥ 1 and lung involvement in elderly patients. Among the analyzed group, lung lesions were more common in patients with late-onset rather than early-onset disease phenotype. However, as these differences were not statistically significant, there is still the need to monitor young patients for this complication.

Another characteristic symptom of pSS is the inflammation of small joints.[30] Joint involvement was one of the most frequent clinical manifestations of pSS in our patients. No differences were noted concerning the frequency of musculoskeletal system involvement depending on age, in line with reports from other researchers.[5] Articular involvement occurred in about half of patients in each subgroup, and should thus be considered as a part of the diagnostics of patients with arthritis and a significant RF titer.

Renal involvement in the course of pSS is rarely observed, i.e., it presents in less than 10% of patients. Infiltration of the kidney by plasma cells is a key feature and is similar to lymphoplasmacytic infiltration of the salivary glands.[31] In our group of patients, renal changes occurred sporadically and only in patients with early onset of the disease. These findings are in line with a study by Jain et al. concerning renal involvement in pSS patients, where renal involvement was mainly observed in young people with symptoms of sicca.[32] Unlike the cited work, in our patient sample, renal changes were not associated with more frequent arthritis. However, the small proportion of patients with this complication (4%) prevents more detailed conclusions from being drawn.

Limitations

One of the limitations of the present study is the small group of patients with late and early onset of the disease, which results from the natural course of pSS. Moreover, the follow-up time was relatively short (36 months on average). Long-term follow-up is particularly crucial due to SLE and pSS coexistence at older age.

Conclusions

Based on the findings of this study, about 30% of pSS patients present with the early or late phenotype of the disease. Patients with early-onset pSS differed from those with late-onset pSS only in a higher incidence of peripheral lymphadenopathy and cytopenia. This observation has significant clinical implications as it draws attention to the need for diagnostics of pSS in young patients with organ manifestations and dryness symptoms, which are not always strongly expressed. The involvement of the lung and joints is common in pSS regardless of patient age. The observed quantitative differences (although statistically nonsignificant) in the prevalence of lung lesions in patients with the late-onset phenotype suggest the need to verify our observations in larger samples of patients. There was no difference in the frequency of lymphocytic FS infiltrations in patients ≥65 compared to ≤35 years of age, as there were no statistically significant differences in patients' serological profiles.

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References

1. Kaminski B. Laryngological manifestations of Sjögren's syndrome. *Reumatologia*. 2019;57(1):37–44. doi:10.5114/reum.2019.83237
2. Ramos-Casals M, Brito-Zeron P, Siso-Almirall A, Bosch X. Primary Sjögren's syndrome. *BMJ*. 2012;344:e3821. doi:10.1136/bmj.e3821
3. Qin B, Wang J, Yang Z, et al. Epidemiology of primary Sjögren's syndrome: A systematic review and meta-analysis. *Ann Rheum Dis*. 2015; 74(11):1983–1989. doi:10.1136/annrheumdis-2014-205375

4. Stefanski AL, Tomiak C, Pleyer U, Dietrich T, Burmester GR, Dörner T. The diagnosis and treatment of Sjögren's syndrome. *Dtsch Arztebl Int*. 2017;114(20):354–361. doi:10.3238/arztebl.2017.0354
5. Tishler M, Yaron I, Shirazi I, Yaron M. Clinical and immunological characteristics of elderly onset Sjögren's syndrome: A comparison with younger onset disease. *J Rheumatol*. 2001;28(4):795–797. PMID: 11327252
6. Koh ET, Boey ML. Late onset lupus: A clinical and immunological study in a predominantly Chinese population. *J Rheumatol*. 1994; 21(8):1463–1467. PMID:7983647
7. Stevens MB. Connective tissue disease in the elderly. *Clin Rheum Dis*. 1986;12(1):11–32. PMID:3522080
8. Ramos-Casals M, Cervera R, Font J, et al. Young onset of primary Sjögren's syndrome: Clinical and immunological characteristics. *Lupus*. 1998;7(3):202–206. doi:10.1191/096120398678920019
9. Singh AG, Singh S, Matteson EL. Rate, risk factors and causes of mortality in patients with Sjögren's syndrome: A systematic review and meta-analysis of cohort studies. *Rheumatology*. 2016;55(3):450–460. doi:10.1093/rheumatology/kev354
10. Parisis D, Chivasso C, Perret J, Soyfoo MS, Delporte C. Current state of knowledge on primary Sjögren's syndrome, an autoimmune exocrinopathy. *J Clin Med*. 2020;9(7):2299. doi:10.3390/jcm9072299
11. Ramos-Casals M, Solans R, Rosas J, et al; GEMESS Study Group. Primary Sjögren's syndrome in Spain: Clinical and immunologic expression in 1010 patients. *Medicine (Baltimore)*. 2008;87(4):210–219. doi:10.1097/MD.0b013e318181e6af
12. Brito-Zerón P, Acar-Denizli N, Ng WF, et al; Sjögren Big Data Consortium. Epidemiological profile and north-south gradient driving baseline systemic involvement of primary Sjögren's syndrome. *Rheumatology (Oxford)*. 2020;59(9):2350–2359. doi:10.1093/rheumatology/kez578
13. Shiboski CH, Shiboski SC, Seror R, et al; International Sjögren's Syndrome Criteria Working Group. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A consensus and data-driven methodology involving three international patient cohorts. *Arthritis Rheumatol*. 2017;69(1):35–45. doi:10.1002/art.39859
14. Fisher BA, Jonsson R, Daniels T, et al; Sjögren's histopathology workshop group (appendix) from ESSENTIAL (EULAR Sjögren's syndrome study group). Standardisation of labial salivary gland histopathology in clinical trials in primary Sjögren's syndrome. *Ann Rheum Dis*. 2017;76(7):1161–1168. doi:10.1136/annrheumdis-2016-210448
15. Seror R, Bowman SJ, Brito-Zeron P, et al. EULAR Sjögren's syndrome disease activity index (ESSDAI): A user guide. *RMD Open*. 2015;20; 1(1):e000022. doi:10.1136/rmdopen-2014-000022
16. Goules AV, Argyropoulou OD, Pezoulas VC, et al. Primary Sjögren's syndrome of early and late onset: Distinct clinical phenotypes and lymphoma development. *Front Immunol*. 2020;11:594096. doi:10.3389/fimmu.2020.594096
17. Witte T. Sjögren-Syndrom [in German]. *Z Rheumatol*. 2019;78(6):511–517. doi:10.1007/s00393-019-0625-8
18. Zhang NZ, Shi CS, Yao QP, et al. Prevalence of primary Sjögren's syndrome in China. *J Rheumatol*. 1995;22:659–661. PMID:7791159
19. Zhao Y, Li Y, Wang L, et al. Primary Sjögren syndrome in Han Chinese. *Medicine (Baltimore)*. 2015;94(16):e667. doi:10.1097/MD.0000000000000667
20. Namkoong E, Lee SW, Kim N, Choi Y, Park K. Effect of anti-muscarinic autoantibodies on leukocyte function in Sjögren's syndrome. *Mol Immunol*. 2017;90:136–142. doi:10.1016/j.molimm.2017.07.007
21. Jayakanthan K, Ramya J, Mandal SK, Sandhya P, Gowri M, Danda D. Younger patients with primary Sjögren's syndrome are more likely to have salivary IgG anti-muscarinic acetylcholine receptor type 3 antibodies. *Clin Rheumatol*. 2016;35(3):657–662. doi:10.1007/s10067-016-3186-0
22. Haga HJ, Jonsson R. The influence of age on disease manifestations and serological characteristics in primary Sjögren's syndrome. *Scand J Rheumatol*. 1999;28(4):227–232. doi:10.1080/03009749950155599
23. Ingegnoli F, Castelli R, Gualtierotti R. Rheumatoid factors: Clinical applications. *Dis Markers*. 2013;35(6):727–734. doi:10.1155/2013/726598
24. Shiboski SC, Shiboski CH, Criswell LA, et al. American College of Rheumatology Classification Criteria for Sjögren's Syndrome: A data-driven, expert consensus approach in the SICCA cohort. *Arthritis Care Res (Hoboken)*. 2012;64(4):475–487. doi:10.1002/acr.21591
25. Baldini C, Ferro F, Luciano N, Bombardieri S, Grossi E. Artificial neural networks help to identify disease subsets and to predict lymphoma in primary Sjögren's syndrome. *Clin Exp Rheumatol*. 2018;112(3):137–144. PMID:30156549
26. Sebastian A, Madej M, Sebastian M, et al. Prevalence and clinical presentation of lymphoproliferative disorder in patients with primary Sjögren's syndrome. *Rheumatol Int*. 2020;40(3):399–404. doi:10.1007/s00296-020-04522-7
27. Brito-Zerón P, Retamozo S, Gandía M, et al. Monoclonal gammopathy related to Sjögren syndrome: A key marker of disease prognosis and outcomes. *J Autoimmunol*. 2012;39(1–2):43–48. doi:10.1016/j.jaut.2012.01.010
28. Anquetil C, Hachulla E, Machuron F, et al. Is early-onset primary Sjögren's syndrome a worse prognosis form of the disease? *Rheumatology*. 2019;58(7):1163–1167. doi:10.1093/rheumatology/key392
29. Kakugawa T, Sakamoto N, Ishimoto H, et al. Lymphocytic focus score is positively related to airway and interstitial lung diseases in primary Sjögren's syndrome. *Respir Med*. 2018;137:95–102. doi:10.1016/j.rmed.2018.02.023
30. Mirouse A, Séror R, Vicaut E, et al. Arthritis in primary Sjögren's syndrome: Characteristics, outcome and treatment from French multicenter retrospective study. *Autoimmunol Rev*. 2019;18(1):9–14. doi:10.1016/j.autrev.2018.06.015
31. François H, Mariette X. Renal involvement in primary Sjögren syndrome. *Nat Rev Nephrol*. 2016;12(2):82–93. doi:10.1038/nrneph.2015.174
32. Jain A, Srinivas BH, Emmanuel D, et al. Renal involvement in primary Sjögren's syndrome: A prospective cohort study. *Rheumatol Int*. 2018;38(12):2251–2262. doi:10.1007/s00296-018-4118-x