Current Rheumatology Research

Montaño-Tapia et al, Curr Rheumatol Res. 2024;4(1):11-18.

Research Article

35 years follow-up of primary Sjogren's syndrome: A single center study

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Received date: May 03, 2023
Accepted date: June 04, 2024

Citation: Montaño-Tapia L, Yildrim R, Abrantes AM, Isenberg D. 35 years follow-up of primary Sjogren's syndrome: A single center study. Curr Rheumatol Res. 2024;4(1):11-18.

Abstract

Objectives: We studied a cohort of Sjögren's syndrome patients followed at a single centre for over 35 years, analyze their outcomes during the course of the disease.

Methods: A cohort of 232 patients with primary Sjögren's syndrome was retrospectively assessed at University College London Hospital, UK, over a very long period to capture the evolving features and complications of the disease and to focus on the causes of death.

Results: The mean age at diagnosis was 50.5 years (SD=14.78 years). The mean years of follow-up since diagnosis was 12.1 years (SD= 8.65); 48 patients (20.7%) were lost to follow-up at some point. Lymphoma developed in 20 patients. When compared with the rest of the patients, the incidence of glandular manifestations was higher in the lymphoma group (11 [55%] vs 59 [37.8%]; p=0.005). In independent multivariate regression analysis, parotid swelling at the time of diagnosis was the most important predictive factor. We compared patients between <15 and >15 years of follow-up and found a statistically significant difference in arthritis (p=0.010), Raynaud's phenomenon (p ≤ 0.001), and vasculitis (p=0.013). The majority of lymphomas developed <15 years post-diagnosis (8.6% vs 5.5%). Thirty-seven patients (20%) died, with a mean age of 80.20 years old (SD=8.547); infection was the main cause of death (11 out of 24 causes of death were identified).

Conclusion: This very long-term follow-up (>35 years) shows that the main complication associated with Sjögren's syndrome was related to lymphoma, which tends to develop during the first years of the disease. In contrast, in our cohort among those patients who died, the majority were over 70 years old (mean age of death was 80.20 years), confirming that the disease is clearly compatible with a long-life expectancy.

Keywords: Sjogren's syndrome, long-term effects, follow-up studies, lymphoma

Abbreviations: ANA: Antinuclear Antibodies; CNS: Central Nervous System Disease; DLBCL: Diffuse Large B-cell Lymphoma; EULAR: European Alliance of Associations for Rheumatology; ILD: Interstitial Lung Disease; MALT: Mucosa-Associated Lymphoid Tissue; MGUS: Monoclonal Gammopathy of Unknown Significance; NHL: Non-Hodgkin's Lymphomas; PNS: Peripheral Nervous System Disease; pSS: Primary Sjögren's Syndrome; RF: Rheumatoid Factor; RNP: Anti-Ribonucleoprotein

Introduction

Primary Sjögren's syndrome (pSS) is an autoimmune rheumatic disease characterized by a lymphocytic infiltration of exocrine glands [1]. It mostly becomes apparent in women between 40 and 60 years old [2]. Its clinical manifestations are heterogeneous, ranging from sicca syndrome to extra glandular manifestations [3].

Its serological features include anti-Ro/SSA and anti-La/SSB antibodies which are characteristic markers, present in 60-80% of patients [4]. These may be present for 20 years before the onset

of the symptoms [5]. Anti-nuclear antibodies (ANA) (up to 80%), rheumatoid factor (RF) (approximately 50%), and hypergammaglobulinaemia (reported to be present in 22-42% of the patients) are also found frequently in these patients [6-9]. Salivary gland biopsy is a useful, though invasive procedure that remains the gold standard for capturing the diagnosis [10,11].

The most common features of this syndrome are xerostomia and keratoconjunctivitis sicca. In about 30% of cases, unilateral or bilateral parotid enlargement may occur [12]. Arthralgia is one of the most common complaints [13]. Pulmonary manifestations including tracheal, bronchiolar, and pulmonary involvement, including interstitial lung disease (ILD) are present in 3 to 11% of patients [14]. Renal involvement comprises tubulointerstitial nephritis and glomerular disease [15]. Among neurological complications, described in 10-60% of cases, the most frequent is mixed motor/sensory or pure sensory neuropathy [16]. Cutaneous features include annular erythema, cutaneous vasculitis, cutaneous purpura, and ulcers [17]. An association between Sjögren's syndrome with autoimmune thyroid disease [18] and celiac disease [19] has also been described.

These patients have an increased risk of lymphoma, 10 to 44 times higher than the general population [2]. This is mostly probably due to the constant stimulation of B cells by autoantigens present in the exocrine glands and other mucosa-associated lymphoid tissue (MALT) [20]. In this context, the most common lymphomas are non-Hodgkin's lymphomas (NHL) [21], notably MALT lymphoma, diffuse large B-cell lymphoma (DLBCL), and marginal zone lymphoma [22,23]. Furthermore, there is also a higher risk of solid organ neoplasms [23].

Evidence in the literature regarding the systemic manifestations of this syndrome, especially over very long periods of follow-up is limited, as many of the studies were carried out with a small number of patients [24] with a short follow-up time, invariably less than 15 years [25,26]. Although a recent major international effort has characterized thousands of patients [27], this study also lacks longitudinal data evaluation, restricting extrapolation of the results. There have been very few attempts to capture really long-term (>20 years) follow-up in patients with Sjögren's syndrome [25]. Studies reporting the causes of death in Sjögren's syndrome are also very limited. The main causes of death described include lymphoma and solid organ neoplasms, infections, and cardiovascular diseases [28-36].

Here we have aimed to determine what happens to Sjögren's patients over a very long period of follow-up (up to 38 years), analyzing the main demographic, laboratory, clinical characteristics, morbidity, and mortality in >230 primary Sjögren's patients followed in the Centre for Rheumatology, University College London Hospital (UCLH).

Materials and Methods

Patient selection

All patients who were diagnosed with Sjögren's syndrome and under care between 1984 and December 2022 were retrospectively screened. To be included in the analysis, sufficient data to ensure that the patients met the latest version of the European Alliance of Associations for Rheumatology (EULAR) classification criteria (2016) for pSS was required [4]. Those who had secondary SS were excluded. The authors retrospectively reviewed the case notes, computer records, and primary healthcare databases on an audit basis. Demographic features including age at diagnosis, sex, race (Caucasian, black African, African– Caribbean, South Asian, mixed, and other), years of follow-up and outcome (alive, dead, lost to follow-up), serological parameters (antinuclear antibody [ANA], rheumatoid factor, anti-Ro/SSA, anti-La/SSB, anti-ribonucleoprotein [RNP]), biopsy status (minor salivary gland lip biopsy) and clinical features were analyzed. Clinical features were categorized into glandular manifestations (parotid swelling, lymphadenopathy) and extra-glandular manifestations (non-erosive arthritis, Raynaud's phenomenon, central and peripheral nervous system [CNS and PNS] disease). Other autoimmune disorders which were diagnosed at least one year after pSS diagnosis were recorded. These included thyroid (hypo-and hyperthyroidism confirmed as autoimmune, autoimmune thyroiditis), dermatological (cutaneous lupus, psoriasis, vitiligo), gastrointestinal (celiac disease, pernicious anaemia, ulcerative colitis), and other autoimmune rheumatic diseases (systemic lupus erythematosus, rheumatoid arthritis, antiphospholipid syndrome, rheumatoid arthritis, and polymyalgia rheumatica). Haematological disorders were classified as hypergammaglobulinemia and hypogammaglobulinemia, monoclonal gammopathy of unknown significance (MGUS) and autoimmune cytopenias including lymphopenia, neutropenia, and thrombocytopenia.

Common comorbid conditions (osteoarthritis, osteopenia, osteoporosis, and cardiovascular events) either before or after primary SS diagnosis, and data regarding solid tumors and lymphoma development after the diagnosis of pSS were also recorded. Among the patients who had died, the cause of death, if known, was noted. The patients who were diagnosed initially in an external center then followed in our department and those lost to follow-up were also recorded. Duration for these patients was also noted from the first admission to our center to the last visit and/or death.

Statistical analysis

Descriptive statistics were used for epidemiological, serological, and clinical features. Frequencies and percentages were used for categorical variables and mean (standard deviation [SD]) was used for continuous variables. A univariant analysis ($\chi 2$ and Fisher's tests) was used to compare the patients who developed lymphoma with those who did not. A multivariant analysis was used for statistically significant features. Logistic regression and bivariant analysis were also performed to avoid the presence of confounding variables and calculate the adjusted OR (odds ratio) and 95% confidence interval (95% CI). A p-value of <0.05 was considered as significant.

Results

General characteristics

Our cohort included 232 patients. Clinical characteristics are summarized in **Table 1**. Caucasian (61.6%) was the most common ethnic origin followed by South Asian (12.5%) and black African (8.2%). The majority of patients were female (94.8%). The mean age at diagnosis was 50.5 years (SD=14.78 years). The mean years of follow-up since diagnosis was calculated as 12.1 (SD= 8.65, ranging from 1 year to 38 years); 48 patients (20.7%) were lost to follow-up at some point during the study period. Of the remaining 184 patients, 37 (20.1%) died during this period. Salivary gland biopsy was performed nearly in half of the patients (47.4%). ANA positivity

was the most frequent serological finding (84%), followed by anti-Ro/SSA antibodies (73%), rheumatoid factor (68%), and anti-La/SSB antibodies (41%). Of the glandular manifestations (n=70, 33.8%) present at the time of diagnosis, parotid swelling was the most common (28.5%) feature followed by lymphadenopathy (15.6%). Raynaud's phenomenon, rash, arthritis, and vasculitis were seen in 34.7%, 30.6%, 27.3%, and 8.6% of patients, respectively. Sixty-five percent of patients showed elevated serum gammaglobulin levels. Lung involvement was seen in 19 patients (8.2%), with pulmonary fibrosis being the most common feature (n=10), followed by bronchiectasis (n=7), and pulmonary hypertension (n=3). Autoimmune hepatitis and primary biliary cirrhosis were seen in 8 (3.4%) and 7 (3%) patients, respectively. Among other comorbidities, osteoarthritis was the most frequent, seen in 32.8% of patients. Lymphoma developed in 20 patients (8.6%), almost all being non-Hodgkin lymphoma (19/20). Other tumors during the period of study were seen in 30 (12.9%) of patients: seven breast cancer, four basal cell carcinoma of the skin, three bladder cancer, two each with pancreatic cancer, melanoma, squamous cell carcinoma of the lung, oropharyngeal carcinoma, and thyroid cancer, and six other tumors (one each with chronic leukocytic leukemia, cervical, ovarian, mesothelioma, pituitary adenoma, myeloma).

Table 1. General characteristics of primary Sjögren's syndrome patients.

Parameters	**n (%); 232**
Age at diagnosis (mean ± SD)	50.5 ± 14.78
Female/Male	220/12 (94.8)
Race	217/232
- Caucasian	143 (61.6)
- Asian	29 (12.5)
- Black-African	19 (8.2)
- Afro-Caribbean	6 (2.6)
- Mixed	4 (1.7)
- Other	16 (6.9)
Years of follow-up (mean ± SD)	12.1 ± 8.65
Clinical characteristics	
- Parotid swelling at diagnosis	59/205 (28.5)
- Lymphadenopathy at diagnosis	32/205 (15.6)
- Arthritis	63/231 (27.2)
- Raynaud's phenomenon	82/230 (34.7)
- Rash	71/232 (30.6)
- Ulcers	39/231 (16.8)
- Vasculitis	20/231 (8.6)
- Hematologic features	
• Hypergammaglobulinemia	99/151 (65.5)
• Hypogammaglobulinemia	8/151 (5.2)
• Neutropenia	4/86 (4.6)
• Lymphopenia	15/86 (17.4)
• Thrombocytopenia	4/86 (4.6)
• MGUS	5/86 (5.8)
- Lung manifestation	19/232 (8.2)
• Pulmonary fibrosis	10 (4.3)
• LIP	1 (0.4)
• Bronchiectasis	7 (3)
• Pulmonary hypertension	3 (1.2)
- Liver involvement	15/232 (6.4)
• Autoimmune hepatitis	8 (3.4)
• Primary biliary cirrhosis	7 (3)
- Central nervous system involvement	8/231 (3.4)
- Peripheral nervous system features	42/232 (18.1)
• Carpal tunnel syndrome	25 (10.7)
• Small fiber neuropathy	2 (0.8)
• Non-specific peripheral neuropathy	10 (4.3)
• Other	5 (2.1)
Serological parameters	
- ANA positivity	179/212 (84)
- Anti-Ro/SSA	157/215 (73)
- Anti-La/SSB	89/215 (41)
- Rheumatoid factor positivity	121/176 (68)
- RNP	8/215 (3)
Biopsy status	
- Positive findings	107/110 (97)
- Negative findings	3/110 (3)
- Not done	122
Other common comorbidities	
- Osteoarthritis	76/232 (32.8)
- Osteopenia	6/232 (2.6)
- Osteoporosis	34/232 (14.6)
- Serious infection	32/232 (13.8)
Outcome	
- Still on follow-up	147 (79.9)
- Deceased	37 (20.1)
- Lost to follow-up	48 (20.7)
Lymphoma development	20/232 (8.6)
- Hodgkin lymphoma	1 (0.43)
- Non-Hodgkin lymphoma	19 (8.1)
• MALT	12 (5.1)
• Others	7 (3)
Other tumors	30 (12.9)

Lymphoma development

Patients diagnosed with lymphoma were compared with all the other patients (**Table 2**). Parameters including sex, age at diagnosis, Caucasian ethnicity, duration of disease, and serological characteristics did not show any statistically significant differences. However, the incidence of glandular manifestations was significantly higher in the lymphoma group (11 [55%] vs 59 [37.8%]; p=0.005). The frequency of hypergammaglobulinemia, vasculitis, and Raynaud's phenomenon were not statistically significantly different.

Table 2. Primary Sjögren's syndrome patients with or without lymphoma diagnosis.

Characteristics	Primary SS with NHL	Primary SS without NHL	P value
Total, n, (%)	20	212	
Age at diagnosis (mean ± SD)	49.7 ± 13.58	50.62 ± 14.9	0.810
Female/Male	20/0	200/12	0.606
Caucasian vs non-Caucasian	12/8	131/66	0.392
Years of follow-up (mean ± SD)	10.88 ± 7.65	12.25 ± 8.73	0.543
ANA positivity	16 (80)	163 (76.9)	0.283*
Anti-Ro	13 (65)	144 (67.9)	0.058
Anti-La	8 (40)	81 (38.2)	0.060
Rheumatoid factor positivity	10 (50)	111 (52.4)	0.143*
Biopsy positivity	8 (40)	99 (46.7)	0.708*
Hypergammaglobulinemia	11 (55)	88 (41.5)	0.661*
Glandular involvement	11 (55)	59 (37.8)	**0.005**
Parotid swelling at diagnosis	10 (50)	49 (23.1)	**<0.001***
Lymphadenopathy at diagnosis	4 (20)	28 (13.2)	**0.013***
Raynaud's phenomenon	6 (30)	76 (35.8)	0.206*
Vasculitis	4 (20)	16 (7.5)	0.159*
Death	7 (35)	30 (14.2)	0.120*

*Fischer's exact test was performed.

Mortality rates were not significantly different between the two groups (p=0.120). In the multivariant analysis, the adjusted risks for the development of lymphoma were calculated in patients with glandular manifestations (OR=4.92, 95% CI 1.63–14.79; p=0.005), parotid swelling at diagnosis (OR=5.75, 95% CI 1.87–17.68; p<0.001), and lymphadenopathy at diagnosis (OR=2.32, 95% CI 0.68–7.94; p=0.013), respectively. In independent multivariate regression analysis, parotid swelling at the time of diagnosis was found to be the most important predictive factor of lymphoma development (p=0.007).

Long-term outcome

Among 232 patients, 147 were still being followed up when the current assessment was undertaken. 37 (20%) of our patients are known to have died. The mean age of death was 80.20 years (SD=8.547) and the mean follow-up years from diagnosis to death was calculated to be 19.57 (SD=9.33, from 1 to 38 years). The causes of death were obtained in 24 patients. The most common cause of mortality was infection (11/24) followed by malignancy-related (three were lymphoma-related, two solid cancer-related, and one chemotherapy related progressive multifocal leukoencephalopathy). Other causes were cardiovascular events in three (stroke, myocardial infarction, and ruptured aortic aneurysm), one severe Parkinson's disease related complication, and due to natural causes in two. No statistical significance between the living and deceased patients was found in terms of parotid swelling and lymphadenopathy at the time of diagnosis, gender, central and peripheral nervous system involvement, and lymphoma development. Caucasians were found to be statistically more prone to dying (p<0.001) than other ethnic groups. Lung involvement was statistically higher among the deceased patients (p= 0.007) (**Table 3**). 73 patients have been followed for more than 15 years. Within this group, arthritis (p=0.010), Raynaud`s phenomenon (p<0.001), and vasculitis (p=0.013) were statistically higher than patients who were followed for less than 15 years (**Table 4**).

Discussion

While many cross-sectional and short-term studies have been published [26,37,38], very little data have been published about very long-term follow-up (over 15 years) post diagnosis of patients with Sjögren's syndrome. There is a dearth of information about very long-term follow-up and causes of death.

We have attempted to address these important questions by observing and describing the behavior of the disease over a very long-term follow-up, focusing on the complications during this period, noting the age at death and its causes and determining any links to the disease itself.

We now describe a cohort of 232 patients followed for a mean of 12.1 years (SD=8.65), over 73 patients (31.4%) of whom have been followed up for >15 years. Our key observations comparing the two groups between short-term (<15 years) and long-term (>15 years) follow-up, are that we have observed statistically significant differences in four characteristics during the course of the disease.

Table 3. Comparison of characteristics between dead and alive patients with primary Sjögren's syndrome diagnosis.

Characteristics	Dead (N:37) (%)	Alive (N: 155) (%)	P value
Gender (F/M)	34/3	150/5	0.11
Caucasian/non-Caucasian	31/5	84/67	**<0.001***
ANA positivity	22 (59.5)	130 (83.9)	**0.001***
Ro positivity	14 (37.8)	125 (80.6)	**<0.001***
La positivity	11 (29.7)	68 (43.9)	**0.002***
RF positivity	13 (35.1)	85 (54.8)	0.073
Hypocomplementemia	1 (2.7)	12 (7.7)	0.294*
Hypergammaglobulinemia	8 (21.6)	75 (48.4)	**0.02***
Glandular involvement	10 (33.3)	53 (37.6)	0.104
Parotid swelling	8 (27.6)	45 (32.4)	0.131
Lymphadenopathy	4 (13.8)	24 (17.1)	0.63
Arthritis	10 (27)	38 (24.5)	0.513*
Raynaud`s	16 (43.2)	51 (32.9)	0.377*
Vasculitis	6 (16.2)	10 (6.5)	0.3*
Lung involvement	8 (21.6)	8 (5.2)	**0.007***
CNS involvement	2 (5.4)	4 (2.6)	0.169*
PNS involvement	8 (21.6)	27 (17.4)	0.832
Liver involvement	3 (8.1)	9 (5.8)	0.777*
Renal tubular acidosis	1 (2.7)	1 (0.6)	0.105*
Lymphoma development	7 (18.9)	10 (6.5)	0.062*
Other malignancy development	8 (21.6)	13 (8.4)	**0.018**

*Fischer's exact test was performed.

Table 4. Comparison between patients followed >15 years versus <15 years of follow-up.

Characteristics	Over>15 years (N:73) (%)	Lower<15 years (N:139) (%)	P value
Arthritis	27 (37)	30 (21.6)	**0.010***
Raynaud`s	37 (50.7)	38 (27.3)	**<0.001***
Vasculitis	10 (13.7)	6 (4.3)	**0.013***
Lung involvement	7 (9.6)	10 (7.2)	0.542*
CNS involvement	3 (4.1)	3 (2.2)	0.625*
PNS involvement	16 (21.9)	19 (13.7)	0.124
Liver involvement	6 (8.2)	7 (5.1)	0.379*
Renal tubular acidosis	0 (0)	3 (2.2)	0.714*
Lymphoma development	4 (5.5)	12 (8.6)	0.409
Other malignancy development	7 (9.6)	18 (12.9)	0.471
Death	19 (26)	11 (7.9)	**<0.001**

*Fischer's exact test was performed

These characteristics are arthritis (p=0.010), Raynaud's phenomenon (p<0.001), and vasculitis (p=0.013). The fourth characteristic is death, which could be expected given the older age of patients as the follow-up continues. Some of the main complications associated with the disease, such as lung, liver, and neurological involvement, were not associated with any difference between the two periods studied. The development of lymphoma occurred within the group of the first 15 years, but with no statistically significant results (p=0.409). It highlights that no more major complication is associated with longer-term follow-up. Notably, the development of malignancy has tended to be more common in those followed for shorter periods, however, in our cohort, this was not statistically significantly different.

In the largest multi-center cross-sectional study published to date, Brito-Zerón *et al.* [27] analyzed a cohort of 10,500 patients with pSS, reporting that 93% were females with a mean age at diagnosis of 53.1 years, similar to our study (female 94.8%, mean age 50.5 ±14.78 years). The main serological findings (ANA, anti-Ro/SSA, anti-La/SSB) at the time of diagnosis correlated with the previous studies [27], with the exception of RF which showed a higher prevalence in our study with 68% of the patients being positive.

In patients diagnosed with pSS, the risk of developing B-cell lymphoma is significantly higher than in the rest of the population [39]. The original claim of Kassan *et al.* [40] in 1978 was that the risk was 44 times higher than in the general population. Subsequent studies have confirmed this finding. The UCLH cohort in 2006 [41] reported that the increased risk was 37.5 times. In contrast, a lower increased prevalence has been noted in other studies. Thus, in a study done in Taiwan [42] with a large cohort of 7852 patients, the prevalence of lymphoma associated with pSS was 7.08 times higher. In the present study, lymphoma was diagnosed in 20 patients (8.6%). Retamozo *et al.* [2] summarized the different prevalence between studies and suggested that the variation might be due to the design of the study.

At diagnosis, different serological patterns and clinical presentations of pSS may be risk factors for the development of lymphoma-related disease. We found that parotid swelling and lymphadenopathy at diagnosis demonstrated a statistically significant difference that was confirmed in the multivariant analysis (parotid swelling (OR=5.75, 95% CI 1.87–17.68; p<0.001), and lymphadenopathy (OR=2.32, 95% CI 0.68–7.94; p=0.013). Other serological alterations are mentioned as risk factors, such as hypocomplementemia [43], which was not analyzed in this study mainly due to a lack of data.

Other malignancies were noted (30 patients– 12.9%), as described in earlier studies [44]. Given the relatively old population among our Sjögren's cohort, this is not surprising. Similarly, the frequency of osteoarthritis (76 patients, 32.8%) and osteoporosis (34 patients, 14.6%,) was to be expected.

The development of complications during the long follow-up was noted. We observed pulmonary involvement in 19 patients (8.2%), slightly less than has been described before [45]. The neurological domain is a common extra-glandular manifestation mainly due to peripheral nervous system involvement [16]. In our cohort, 18.1% of the patients had peripheral nervous system involvement, due mainly to carpal tunnel syndrome (25 patients, 10.78%). Primary biliary cirrhosis and autoimmune hepatitis are manifestations that have been recognized to be associated with pSS. In our cohort, they were present in 3% and 3.4% of the patients respectively, which is comparable with prior data [46].

We noted 37 (20.1%) deaths among our cohort. We compared the main characteristics between the deceased and the living patients, observing a significant statistical difference mainly in lung involvement (p=0.007), where it was present in 8 (21.6%) deceased patients and 8 (5.2%) among those still living. This was also noted in the systematic review and meta-analysis reported by Huang *et al.* [26].

The mean age of death was 80.20 years (SD=8.547). The main causes of death observed were infection and malignancy related, which was already observed in other studies [25]. However, we could not reliably determine the cause of death in 13 out of 37 patients. Interestingly though, unlike other classic autoimmune rheumatic diseases, notable Systemic Lupus Erythematosus [47,48] and Rheumatoid Arthritis [49,50], no obvious increase in cardiac disease or as cause of death was evident in our Sjögren's cohort.

We are aware of weaknesses in the study. It is single-center, and the clear majority of patients were from one ethnic group. 20.7% were lost in follow-up. However, this invariably occurred after they had been followed for a long period. There were some, though limited, missing data. Other factors, beyond those considered in our study, such as food quality and exercise may well contribute to aspects of longevity, it would be interesting in the future to consider these aspects. The main strength of this study is the long and careful follow-up over periods of up >35 years. We assume that some of our very elderly patients were simply too frail to keep their Sjögren's clinic appointments.

In addition, previous studies used the prior existing classification criteria for pSS, which could have led to different results.

Finally, this study analyzes the data of a really long-term follow (over 35 years) in patients with primary Sjögren's syndrome, concluding that the main complication during the course of the disease is the development of lymphoma. At the same time, the main causes of death are not related to the disease and it is clearly compatible with a long life expectancy.

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