Impact of time to diagnosis in patients with primary Sjögren's syndrome: a cross-sectional study

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Abstract

Objective

Primary Sjögren's syndrome is a chronic autoimmune disease with an inflammation of exocrine glands. It can be difficult to diagnose due to frequently unspecific symptoms, such as fatigue and myalgia. The aim of this study was to investigate the journey of patients prior to the diagnosis of primary Sjögren's syndrome and how this affects the patient-reported outcomes.

Methods

The study included 170 patients from the outpatient clinic with an age of at least 18 years that were diagnosed with primary Sjögren's syndrome (ICD-10 M35.0) and fulfilled ACR/EULAR 2016 criteria at least 12 months before. Socio-demographic details, patient-reported outcomes and the history of diagnosis were obtained via a structured questionnaire.

Results

The average diagnostic latency for this group of patients with Sjögren's syndrome is 5.98 years, with a median of 2 years. The cohort was divided into two groups based on the median of two years: one with a longer and the other with a shorter diagnostic delay. The group with a longer diagnostic delay was in a significantly poorer general health condition and was significantly more likely to report a negative impact on the general performance. Patients with longer diagnostic delay reported significantly more physician visits and suffered significantly more frequently from vaginal dryness, gastrointestinal symptoms and breathlessness as initial symptoms.

Conclusion

Our findings underline the importance of awareness of Sjögren's syndrome and interdisciplinary training of physicians to improve the patient-related outcomes due to a reduced diagnostic latency.

Key words

Sjögren's syndrome, patient-reported outcome measures, health services research

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Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disease characterised by inflammation of exocrine glands, such as lachrymal and salivary glands, resulting in sicca symptoms including dry eyes (xerophthalmia) and mouth (xerostomia) (1). Moreover, patients with primary Sjögren's syndrome (pSS) commonly experience non-specific symptoms, such as fatigue in 70% of cases (2) and arthralgia in 48% of cases (3). Prompting the diagnosis can be complicated by these frequent non-specific symptoms (4).

SS predominantly affects females, with a female-to-male ratio of 9:1. Its overall prevalence in Europe ranges from 0.04% to 0.1% (4-6) . pSS is therefore more frequent than other connective tissue diseases, with a prevalence of systemic sclerosis of 0.01-0.035%, systemic lupus erythematosus of 0.015-0.05% and inflammatory myositis of 0.002-0.034% (7-9).

At the onset of the disease, patients often experience unspecific symptoms of Sjögren's syndrome, which can lead to a delay in diagnosis. The average time to diagnosis in 2000 was 6 years (10). In addition, a study conducted by Narváez *et al*. in Spain revealed that nearly half of the patients with pSS were not diagnosed until their survey was conducted, indicating a high rate of undiagnosed patients (11).

According to the Sjögren's Foundation, the time to diagnosis could be shortened by around 50%, thus reducing the diagnostic delay to 2.8 years in 2018 by increased public and health care awareness and education (12, 13). This finding is consistent with two studies conducted in Taiwan and Saudi Arabia, both of which reported a diagnostic delay of 2.2 years each (14, 15). However, the impact of the diagnostic delay of SS on patients' symptoms and everyday life experiences remains unclear.

The primary objective of this study was to gather in-depth information on the patient journey before diagnosis. Furthermore, we wanted to provide evidence on how the delay of diagnosis may impact the patient-reported outcomes of the disease.

Methods

Study design

This cross-sectional monocentric survey was performed at the outpatient clinic of the department of Rheumatology and Immunology, at a large university hospital in Hannover, Germany. A self-developed questionnaire was used to investigate the journey of patients prior to the diagnosis of pSS and how this affects the patient-reported outcomes. The survey was conducted between November 9th 2022 and March 31st 2023.

Eligibility criteria and patient recruitment

The eligibility criteria for patients participating in this study were:

1. clinical diagnosis of pSS (ICD-10 M35.0) by a rheumatologist; 2. pSS diagnosed at least 12 months earlier; 3. age of at least 18 years.

All patients were identified through the department's internal database (n=482). All patients who met the eligibility criteria were invited via regular mail to complete a questionnaire. Finally, we included only participants who met the ACR/EULAR 2016 criteria for SS.

Design of the questionnaire

The questionnaire was developed based on the previously published questionnaire by Unger *et al*. evaluating patient-reported outcomes in pSS patients (16). Finally, the questionnaire was discussed with members of the German support group in rheumatology, the Rheuma-Liga Niedersachsen e.V. The questionnaire was used to record socio-demographic details, patient symptoms, diagnosis course, physician interactions (pre-diagnosis visits, interactions with physicians), as well as current therapy. Patient-reported outcomes were measured using a four-point Likert scale to assess emotional distress, impact on daily life, and general performance. The general health status was evaluated on a numerical scale ranging from 0 to 100. The questionnaire was initially tested for feasibility, comprehensibility, and processing time in the target group using the "verbal probing" method (17).

Table I. Patients characteristics.

Sex (data available in n=170)	
Female	143 (84.1 %)
Male	27 (15.9 %)
Nationality (data available in n=166)	
German	161 (97.0%)
Other	5 (3.0%)
Ethnicity (data available in n=163)	
Caucasian	162 (99.4%)
Other	1 (0.6%)
Educational level (data available in n=166)	
Secondary general school leaving certificate	33 (19.9%)
Intermediate school leaving certificate	63 (38.0%)
University entrance qualification	37 (22.3%)
University degree or higher	33 (19.9%)
Marital status (data available in n=168)	
Single	27 (16.1%)
Married/civil partnership	108 (64.3%)
Divorced	22 (13.1%)
Widowed	11 (6.5%)
General health status	
All patients, mean (n=169)	53.41 (±22.5)
Age [years]	
Actual age (n=170)	60.92 (±14.0)
Age at start of symptoms (n=153)	47.01 (±14.7)
Age at diagnosis (n=167)	53.02 (±13.9)
Latency time (years) n=152	
Mean	5.98 (±9.5)
Median	2.0
ESSPRI	
ESSPRI dryness, mean (n=99)	6.02
ESSPRI fatigue, mean (n=99)	5.54
ESSPRI pain, mean (n=104)	5.19
ESSPRI total, mean, (n=92)	5.46
Major organ involvement (data available in n=145)	
Interstitial lung disease	26/145 (17.9%)
Arthritis	47/145 (32.4%)
Polyneuropathy	48/145 (33.1%)

Participants were asked to complete the questionnaires while verbally reporting all relevant thoughts. Based on the results of the pre-test, the questionnaire was revised again.

Data collection

The patients were contacted by regular mail and following documents were sent: information letters for the study and data protection, the corresponding informed consent forms, the questionnaire with a return envelope. To optimise the response rate, a reminder to fill out the questionnaire was sent after six weeks.

Linking the questionnaires with the medical records

Since the questionnaire provides primarily self-reported outcomes by the patients, the returned questionnaires were linked to the medical records to extract data for the prescribed medication, the ESSPRI scores, ESSDAI scores and for major organ involvement.

Statistical analysis

Statistical tests and descriptive analysis were performed with IBM SPSS Statistics v. 28.0.1.0.

Missing data were restrictively handled. Participants were divided into two groups based on the median diagnostic latency. Based on these binary two groups a Fisher's exact test was performed to assess the effect on the patient-reported outcomes, measured on a Likert-scale. To analyse the ordinary variable ESSPRI and the total number of physician contacts before diagnosis, a Mann-Whitney-U-test was conducted. To calculate the metric variables as age or general health status we performed the Shapiro-Wilk test first, followed by a Mann-Whitney U-test since the data did not follow a normal distribution.

Table II. Visits of physicians before diagnosis.

	All patients		Diagnostic delay > 2 years		Diagnostic delay ≤ 2 years		Fishers exact test ≤/> 2 years	OR ≤/> 2 years
	n=162	% of patients	n=64	% of patients	n=81	% of patients		
General practitioner	130/162	80.2	60/64	93.8	59/81	72.8	<0.001	5.59 [1.82;17.22]
Ophthalmologist	60/162	37.0	30/64	46.9	27/81	33.3	0.124	
Rheumatologist	56/162	34.6	26/64	40.6	27/81	33.3	0.39	
ENT	61/162	37.7	28/64	43.8	28/81	34.6	0.304	
Neurologist	53/162	32.7	22/64	34.4	25/81	30.9	0.722	
Orthopaedist	50/162	30.9	27/64	42.2	21/81	25.9	0.051	
Dentist	51/162	31.5	29/64	45.3	20/81	24.7	0.013	2.53 [1.25;5.12]
Gynaecologist	38/162	23.5	20/64	31.3	15/81	18.5	0.082	
Physiotherapist	37/162	22.8	24/64	37.5	10/81	12.3	<0.001	4.26 [1.85;9.80]
Dermatologist	30/162	18.5	19/64	29.7	10/81	12.3	0.012	3.00 [1.28;7.03]
Pneumologist	23/162	14.2	12/64	18.8	11/81	13.6	0.494	
Endocrinologist	14/162	10.5	12/64	18.8	5/81	6.2	0.035	3.51 [1.17;10.55]
Haematologist	11/162	6.8	6/64	9.4	4/81	4.9	0.337	
Oral Surgeon	12/162	7.4	9/64	14.1	3/81	3.7	0.033	4.26 [1.10;16.44]
Oncologist	5/162	3.1	2/64	3.1	3/81	3.7	1.0	
Other	14/162	8.6	4/64	6.3	9/81	11.1	0.388	

Table III. Patient characteristics in long and short diagnostic delay patients.

		total population	diagnostic latency > 2 years	diagnostic latency ≤ 2 years	Fishers exact test >/≤ 2 years	OR	Mann-Whitney-U	Z
Sex woman	n (%)	143/170 (84.1%)	58/68 (85.3%)	69/84 (82.1%)	p=0.664			
Nationality German	n (%)	161/166 (97.0%)	64/66 (97.0%)	80/83 (96.4%)	p=1.0			
Ethnicity Caucasian	n (%)	162/163 (99.4%)	66/66 (100%)	78/79 (98.7%)	p=1.0			
Age	Mean (SD)	60.92 (±14.0)	61.6 (±12.9)	60.7 (±14.6)			2783.5, p=0.789	-0.269
General health status	Mean (SD)	53.41 (±22.5)	47.58 (±21.9)	56.24 (±22.5)			2159, p=0.013	-2.464
Total physician visits	Mean (SD)	4.0 (±2.9)	5.16 (±3.1)	3.42 (±2.4)			1723.5 p<0.001	-3.49
Pulmonary involvement		26/145 (17.9%)	10/64 (15.6%)	15/67 (22.4%)	p=0.378			
Peripheral nerves involvement		48/145 (33.1%)	22/64 (34.4%)	22/67 (32.8%)	p=0.856			
Joint involvement		47/145 (32.4%)	25/64 (39.1%)	18/64 (26.9%)	p=0.192			
ESSPRI dryness	Mean	6.02	6.02	6.27			955.5 p=0.778	-0.286
ESSPRI fatigue	Mean	5.54	6.09	5.02			766.5 p=0.066	-1.843
ESSPRI pain	Mean	5.19	5.64	4.98			966.0 p=0.295	-1.053
ESSPRI total	Mean	5.46	5.64	5.45			804.5 p=0.741	-0.334
ESSDAI domains								
Constitutional		6/85 (7.1%)	3/38 (7.9%)	2/27 (5.4%)				
Lymphadenopathy		1/85(1.2%)	0/38 (0%)	1/37 (2.7%)				
Glandular		3/85 (3.5%)	1/38 (2.6%)	2/37 (5.4%)				
Articular		10/85 (11.8%)	6/38 (15.8%)	4/37 (10.8%)				
Cutaneous		0/85 (0%)	0/38 (0%)	0/37(0%)				
Pulmonary		11/85(12.9%)	4/38 (10.5%)	7/37 (18.9%)				
Renal		2/85 (2.4%)	0/38 (0%)	2/37 (5.4%)				
Muscular		0/85 (0%)	0/38 (0%)	0/37 (0%)				
PNS		23/85 (27.1%)	7/38 (18.4%)	14/37 (37.8%)				
CNS		0/85 (0%)	0/38 (0%)	0/37 (0%)				
Haematological		33/85 (38.8%)	12/38 (31.6%)	15/37 (40.5%)				
Biological		20/85 (23.5%)	8(38 (21.1%)	8/37 (21.6%)				
ESSDAI total		5.47	4.00	7.16			469.5 *p*=0.012	-2.499

Table IV. Serological markers and ACR/Eular 2016 criteria in the total study population and subgroup analysis.

	Total population	Diagnostic latency > 2	Diagnostic latency ≤ 2 years	Fisher exact test >/≤ 2 years
SS-A positive	97/170 (57.1%)	35/68 (51.5%)	50/84 (59.5%)	p=0.330
SS-B positive	30/167 (18.0%)	9/67 (13.4%)	17/83 (20.5%)	p=0.285
Ro 52 positive	19/141 (13.5%)	7/63 (11.1%)	10/64 (15.6%)	p=0.604
C3c lowered	16/142 (11.3%)	10/63 (15.9%)	6/65 (9.2%)	p=0.294
C4 lowered	6/142 (4.2%)	1/63 (1.6%)	4/65 (6.2%)	p=0.365
Rheumatoid factor positive	40/143 (28.0%)	14/64 (21.9%)	19/65 (29.2%)	p=0.420
Alpha-Fodrin-IgG positive	19/140 (13.6%)	9/61 (14.8%)	9/65 (13.8%)	p=1.0
Positive glandular biopsy (Chisolm-Mason 3 or 4)	95/99 (96.0%)	37/40 (92.5%)	48/49 (98%)	p=0.322
Positive Saxon-Schirmer-Test	162/167 (97%)	66/68 (97.1%)	80/82 (97.6%)	p=1.0
Fulfilled ACR/EULAR 2016 criteria	170/170 (100%)	68/68 (100%)	84/84 (100%)	-

Ethical approval

Following the declaration of Helsinki, approval of the local ethical committee was obtained (approval number 10530_BO_K_2022). The study was registered with the German Register for Clinician Studies (DRKS) under the registration number DRKS00031104.

Results

Patients' characteristics

All the 482 patients visiting our outpatients clinic were invited to participate in this study. Of these patients, 58% returned the survey (n=281). Four patients were excluded because the informed consent was missing. 107 patients were excluded because they did not fulfil the 2016 ACR/EULAR classification criteria for pSS.

The final sample size included 170 patients with pSS. Patient characteristics are shown in Table I. On average, patients were 60.9 (± 14.0) years old and 84.1% were female. The age at the time of symptom onset was 47.0 (± 14.7) years, and the age at the time of diagnosis was 53.0 (± 13.9) years. On average, the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) was 5.46 out of 10 points. Out of the finally included samples, all n=170 questionnaires could be linked to the medical records. Overall, 17.9% of the participants had lung involvement, while arthritis and peripheral polyneuropathy were present in 32.4% and 33.1% of the participants, respectively.

The mean time to diagnosis was 5.98 years (± 9.5) with a median of 2 years. We divided the study population into two groups based on the median of the diagnostic delay: ≤2 years (n=84) and >2 (n=68) until final diagnosis. The group with the shorter delay (≤2 years) is larger, as we also included those 24 participants who reported exactly the median value of 2 years diag-

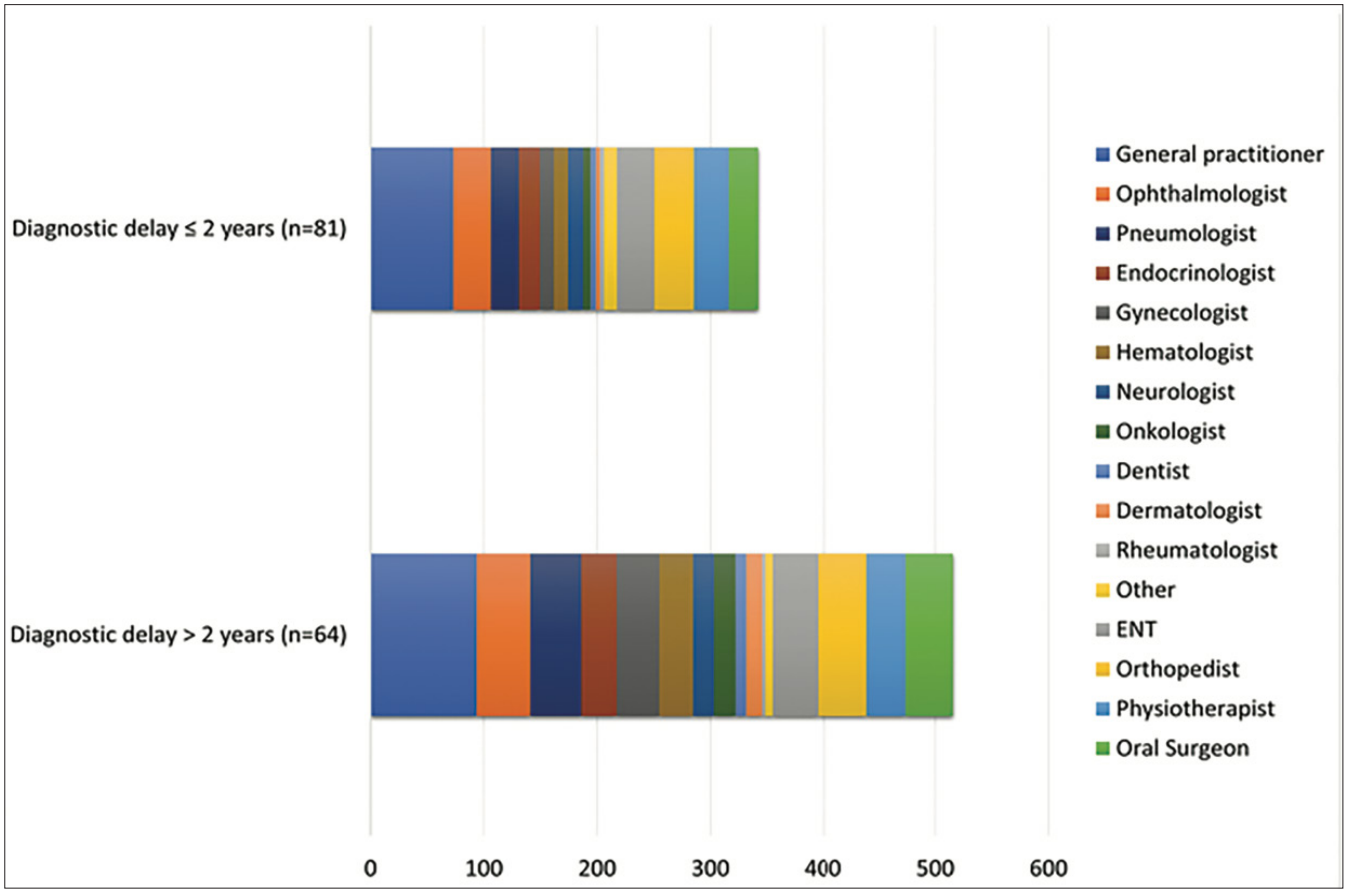

Fig. 1. Physician contacts before diagnosis in % of cases, multiple answers possible.
Number of physician contacts divided according to specialties were visualised with a higher number of contacts in the group of Sjögren's patients with longer diagnostic latency.

nostic delay. There was no statistically significant difference in serological factors, sex, socioeconomic characteristics, major organ involvement or prescribed medication between the groups (Table III and IV, Supplementary Table S1).

Study findings

Physician contacts before diagnosis. In the overall study population, each patient consulted an average of 4.0 physicians. 80.2% of the patients consulted a general practitioner before receiving a diagnosis. Additionally, ophthalmologists (37.0%), ENT physicians (27.7%), neurologists (32.7%) and orthopaedists (30.9%) were visited (Table II).

The data reveal that the group with a longer diagnostic delay had significantly more physician visits (5.16 physician contacts, SD 3.1) compared to the group with a short diagnostic delay (3.42 physician contacts, SD 2.4, U 1723.5, Z -3.49, $p<0.001$) (Fig. 1). Patients who experienced a longer diagnostic delay visited general practitioners ($p<0.001$, OR 5.59), physiotherapists ($p<0.001$, OR 4.26), oral surgeons ($p=0.033$, OR 4.25), dermatologists ($p=0.012$, OR 3.00) and dentists ($p=0.013$, OR 2.53) more frequently than those who experienced a shorter delay (Table II).

The diagnosis of pSS was made by rheumatologists in 65.1% of cases and by neurologists in 17.5%.

- Patient-reported symptoms

The patients initially reported sicca symptoms such as dry eyes (56.6%), dry mouth (51.8%) and dry skin (31.1%). Additionally, non-specific symptoms such as myalgia and arthralgia (54.2%) as well as fatigue (52.4%) were present (Fig. 2 A). In the analysis of the most common complaints related to everyday limitations, an increase in fatigue (62.4%) was observed compared to the initial symptoms. Conversely, typical sicca symptoms such as dry mouth and skin were less frequently reported (47.8% and 16.6%, respectively) (Fig. 2 A). Overall, less symptoms were reported on disease onset by the group of shorter diagnostic delay (Fig. 2 B), while the group of longer diagnostic delay complained more fatigue and myalgia as decisive symptoms for everyday limitations (Fig. 2C). When focusing on the initial symptoms that led to seeking medical attention, the group of longer diagnostic delay reported significantly more frequently vaginal dryness ($p=0.037$, OR 2.34), gastrointestinal symptoms ($p=0.019$, OR 2.43), breathlessness ($p=0.028$, OR 2.48) and skin lesions ($p=0.037$, OR 2.34) (Suppl. Table S2).

- Impact of diagnostic latency

Patients who experienced a longer diagnostic delay (>2 years) reported significantly more difficulties in re-

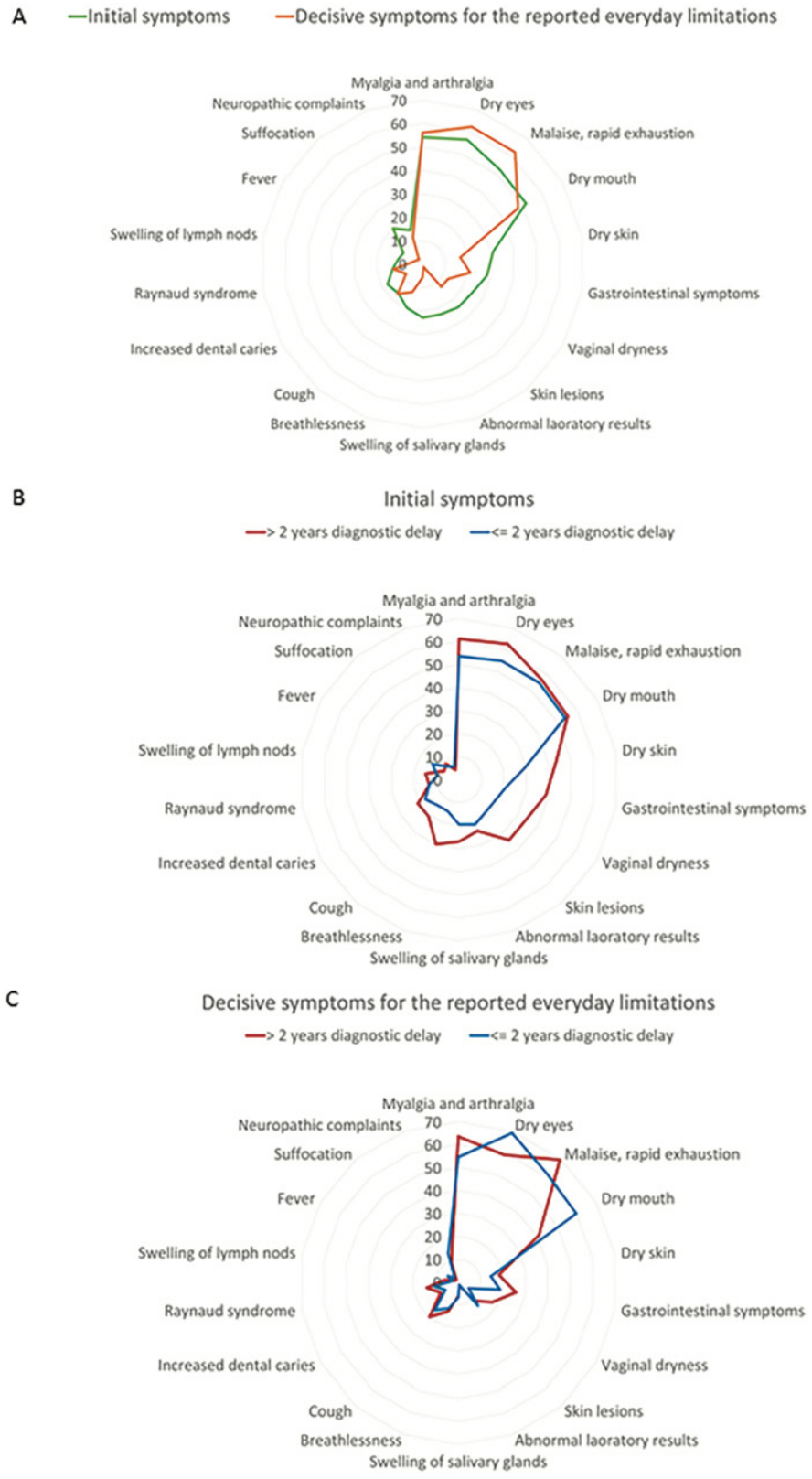

Fig. 2. Patient reported symptoms, comparison of initial symptoms with reported symptoms which are now responsible for the everyday limitations (Figures in percentages).
A: When recording the initial symptoms multiple answers were possible (n=166). To measure the decisive symptoms for the reported limitations, patients could choose their top 5 limiting complaints (n=157).
B: Initial symptoms complained by groups of short (n=82) and long diagnostic delay (n=67).
C: Decisive symptoms complained by groups of short (n=75) and long diagnostic delay (n=66).
All data shown in percentage.

membering details (58.9 %) compared to those with a shorter delay (54.1 %, p=0.042) and the group of longer diagnostic latency is significantly more likely to report that SS has a negative impact on their relationship with their partner (82.0% and 56.7% respectively, p=0.021) (Fig. 3, Suppl. Table S3).
Additionally, a higher percentage of patients with a longer diagnostic delay experienced negative effects on their overall performance (83.3%), compared to those with an earlier diagnosis (60.0%, p=0.008) (Fig. 3, Suppl. Table S3).
Patients who experienced a delay in diagnosis had a numerical general health status that was 8.66 units lower (U=2159, Z=-2.464, p=0.013) (Table III).
There were only slight and non-significant differences of the ESSPRI score (5.64 and 5.45 respectively, U=804.5, Z=-0.334, p=0.741) (Table III) between the groups with long and short diagnostic delay. Even though we have information on the ESSDAI of only a restricted number of participants, we identified a significantly higher total ESSDAI score in patients with shorter diagnostic delay (U=469.5, Z=-2.499, p=0.012) (Table III).

Discussion

This study presents the diagnostic journey of patients with pSS which reveals a mean diagnostic delay of 5.98 years and a median delay of 2.0 years.
The delay is consistent with a recent study conducted in the Arabian and Taiwanese population (14, 15). Due to the prevalence of non-specific symptoms such as fatigue and muscle pain, diagnosing SS can be challenging (18, 1). In this regard, the term occult SS was created to describe cases with non-specific symptoms but not yet typical sicca symptoms (19, 20). Accordingly, a Spanish multicentre study found that 60% of Sjögren's patients had interstitial lung disease, with lung involvement occurring prior to typical sicca symptoms (21). This also corroborates our own findings that one third of patients with pSS and interstitial lung disease were SS-A/Ro negative (22). Therefore, the European League Against Rheumatism (EULAR) recommends the use of multidisciplinary

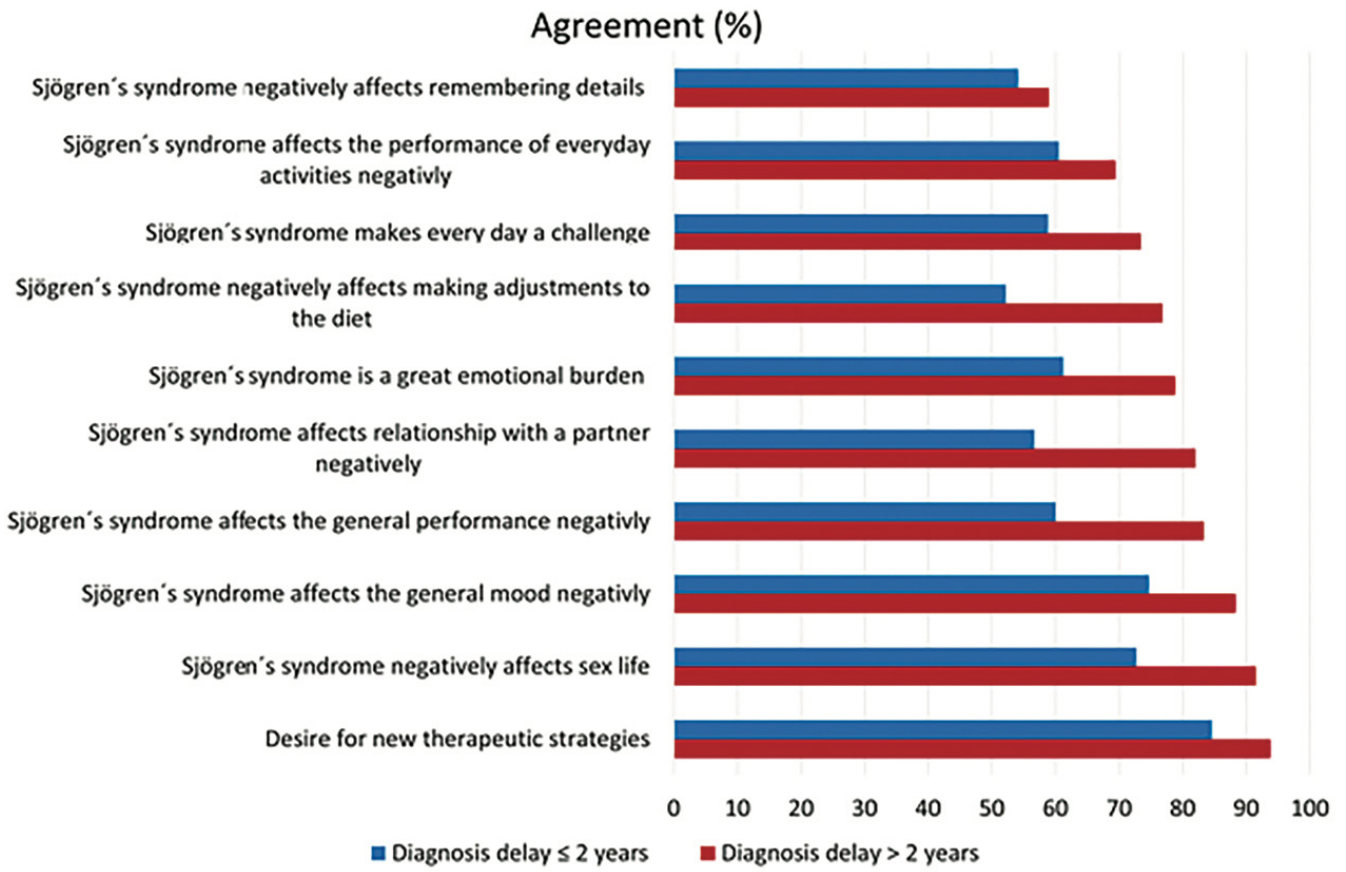

Fig. 3. Patient-reported outcomes in long and short diagnosis delay patients.
Patient-reported outcomes were collected through a questionnaire showed higher percentage of agreement in Sjögren's patients with longer diagnostic delay (red) than in those with shorter diagnostic delay (blue).

teams for the diagnosis and management of pSS, particularly for patients with systemic involvement (23, 20).

We divided our cohort into two groups according to the median of 2 years of diagnostic delay. When focusing on the patient characteristics of both groups, we could not find any differences in major organ involvement, sociodemographic data as gender, age or nationality. Overall, no differences were found in the disease specific medication. When focusing on the ESSDAI, we found a higher disease activity in the group of shorter diagnostic delay. This could be due to the fact that patients with higher disease activity are also more urgent and easier to diagnose. In line with this, a Japanese study was able to show that young age and only dry eyes were a risk factor for delayed diagnosis (24).

Additionally, SS-A/Ro autoantibodies and SS-B/La autoantibodies occurred more frequently in the group of shorter diagnostic delay, even though without statistical significance. It appears, that diagnosing pSS is much easier in the presence of autoantibodies compared to the necessity to perform an invasive glandular biopsy in patients without autoantibodies. This emphasises, that more diagnostic markers in addition to SS-A/Ro and SS-B/La antibodies are needed. New diagnostic markers could improve the early diagnosis of pSS by reducing the group of seronegative pSS (25).

In general, we demonstrated that patients with longer diagnostic delay reported a greater overall symptom burden at onset compared to those with shorter diagnostic delay. Most of these symptoms appear to be unspecific and may mislead the correct diagnosis. This is consistent with recent findings of a link between delayed diagnosis of primary aldosteronism and a higher disease burden (26).

Patients with a longer delay indicated a worse general health status and negative effects on their general performance and their memory ability. This may be the result of the absence of supportive therapy to effectively address symptoms as fatigue in the absence of a definitive diagnosis. Consequently, these symptoms are at risk to becoming chronic.

Regarding fatigue and pain, we measured incongruent results. The items fatigue and pain within the ESSPRI did not differ between the group of longer and shorter diagnostic delay, while patients with longer diagnostic delay were significantly more likely to report malaise, rapid exhaustion and myalgia or arthralgia. This could be due to the nature of the question as the connection with everyday limitations is more tangible for patients. On the other hand, we asked in our questionnaire for a momentary symptom which might be overestimated by the patients whereas in the ESSPRI a two-week period is relevant (27).

The delay in diagnosis has multi-layered consequences for society. Hackett *et al*. found that fatigue, depression and

pain levels correlate with functional disability (28). In general, patients with pSS generally exhibit a lower capacity for everyday activities when compared to the general population (28). In a large Spanish cohort, fatigue was the most common reason why patients with pSS consulted healthcare professionals (29).

In agreement, Lendrem *et al*. evaluated the depression score Euro-QoL-5 dimension (EQ-5D) for patients with pSS. The utility values were significantly increased compared to the general population in the United Kingdom. These values also correlated with standard scores for pain and depression in pSS (30).

To address this impairment, Hackett *et al*. identified seven clusters of key interventions to enhance participation in everyday activities. These interventions include, for example, patient empowerment, improvement in access and coordination of healthcare and public awareness (31). For instance, Longhino *et al*. described several exercise programs to improve fatigue in patients with pSS (32).

Initial symptoms reported by the patients differ between the groups of longer and shorter diagnostic latency. In the group of >2 years of diagnostic latency significantly more vaginal dryness, gastrointestinal symptoms, breathlessness and skin lesions were reported.

Thus, these symptoms could be part of a training programme to gain more attention on the unspecific symptoms of SS to the physicians.

Regarding pre-diagnostic physician visits, patients with a longer diagnostic delay visited physicians significantly more often than patients with earlier diagnosis. Especially, general practitioners, physiotherapists, dermatologists and dentists were contacted in this group significantly more frequently. In comparison to our study, Komori *et al*. recently show that the visit of a department of internal medicine or ophthalmology rises the risk for a delayed diagnosis (24). As a higher utilisation of specialists before diagnosis has an impact of healthcare costs, cost-of-illness studies are needed to estimate the economic burden of this diagnosis delay. In the face of evolving treatment options, it is important to understand how costs are being incurred and what cost savings might occur as a consequence.

As we demonstrated that patients with longer diagnostic delay consulted significantly more physicians than the patients with shorter delay, this might be the main reason for diagnostic delay. A rapid diagnosis is difficult, especially for other specialties, as the symptoms are often non-specific and SS is not well known in all disciplines.

In order to reduce the diagnosis latency, special training could be implemented for the frequently visited physicians. These trainings should also include the aforementioned non-specific symptoms reported more often by the group of longer diagnostic delay.

The study findings, implications and recommendations need to be considered in the context of some limitations. First, data collection was based on a monocentric study at a large university hospital in Germany. The included patients might differ from patients at external outpatients' clinics, for example explaining the more frequent occurrence of organ manifestations. Second, although a rate of 58% of returned questionnaires is considered a high response rate in surveys, a selection bias cannot be ruled out. Next, we retrospectively analysed clinical data with incomplete data collection especially for reporting the ESSDAI. Moreover, we cannot rule out recall bias, as we included participants more than 12 month after their diagnosis and they were then asked to remember the time before their diagnosis. Thus, additional multicentre studies will be needed to investigate the relation of diagnostic latency and clinical outcomes more detailed to improve the clinical care of patients with SS.

To conclude, the study emphasises the negative impact on patient-reported outcomes due to a delay of 5.98 years between the onset of symptoms and the diagnosis of SS. Specifically, a diagnostic delay of more than 2 years was inversely associated with the general reported health status and worsened the effects of SS on patients' overall performance. The study underlines the importance of a higher index of suspicion among physicians routinely involved in investigating such symptoms.

Competing interests

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