

Damage accrual predicts the development of lymphoma in primary Sjögren's disease

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Abstract

Objectives

To study whether damage and its kinetics are associated with mortality and lymphoma development in primary Sjögren's disease (pSjD).

Methods

Single-centre retrospective cohort study including patients with pSjD. Damage was assessed yearly using the Sjögren Syndrome (SS) damage index (DI) (SSDI) and SS Disease DI (SSDDI) scores. Early damage: damage occurring in the first year after diagnosis; early damage increase: increase of ≥ 1 point in the first 5 years. SSDDI and SSDI scores' domains were compared with two-sample test of proportions. Cox regression was performed to investigate predictors of mortality and lymphoma. A $p < 0.05$ was considered statistically significant.

Results

We included 208 patients with pSjD (female: 93.8%; mean age at diagnosis/onset: $49.9 \pm 14.9/45.6 \pm 15.0$ years; mean follow-up time: 14.1 ± 9.2 years). Damage affected 79.3% and 85.1% patients, using SSDDI and SSDI scores, respectively.

Age at diagnosis (per one-unit increase HR 1.1, 95%CI 1.1-1.2) and at onset (per one-unit increase HR 1.1, 95%CI 1.0-1.2) predicted mortality. Damage and early damage increase did not predict mortality with either score.

Seventeen patients (8.2%) developed lymphoma. Early damage increases predicted lymphoma in both scores (SSDDI: HR 14.5, 95% CI 1.8-115; SSDI: HR 12.8, 95% CI 1.5-108.1). Early damage variation, damage variation, and cumulative damage were also predictors of lymphoma.

Conclusions

Although damage was not associated with mortality, age at diagnosis and onset of symptoms were risk factors for mortality in pSjD. Cumulative and evolving damage, especially in the first years of disease, should raise concern about the possible development of lymphoma in these patients.

Key words

Sjögren's disease, mortality, lymphoma

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Introduction

Primary Sjögren's disease (pSjD) is a systemic autoimmune disease characterised by lymphocytic infiltration of exocrine glands (1). The most common features are keratoconjunctivitis sicca and xerostomia. In many patients, slowly evolving organ involvement of varying severity is observed. However, 25% of patients have systemic involvement, with major organ involvement and some develop a non-Hodgkin's lymphoma (NHL) (2-4). Permanent damage may occur as a result of disease activity, concomitant disease or treatment side effects (5).

Damage is an irreversible process, representing a permanent loss of function or structural modification of an organ or system. Outcome measures are critical in determining disease severity and progression and to tailor treatment aimed at more effectively reducing disease activity. However, there is a paucity of validated damage scores for Sjögren's disease (SjD) (6).

The Sjögren Syndrome Disease Damage Index (SSDDI) (7) was developed in a study including 206 patients with a 3-month follow-up period. The index contains 6 domains: ocular, oral, neurological, pulmonary, renal and malignancy.

The Sjögren Syndrome Damage Index (SSDI) (8) utilised the method that led to the development of the SLICC (Systemic Lupus International Collaborating Clinics) criteria for capturing damage in patients with systemic lupus. The first study with this index included only 104 patients followed for 12 months. It contains 10 domains - ocular, oral, neurological, renal, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, endocrinological, and malignancy.

Both damage scoring indices, SSDDI and SSDI, have been analysed elsewhere, highlighting their main strengths and weaknesses (9). The SSDI score clearly distinguishes between items of damage caused by the disease and those arising from comorbidities or therapies. Although sensitivity to change was not tested in the SSDDI, this score emphasises statistical significance between early damage

and damage at 12 months in oral, and ocular domains and also in the total score. Reliability was not tested in either study.

The SSDI was assessed in 60 patients diagnosed with SD followed for a minimum of 1 year (10). No damage was reported in approximately half of the patients. In addition, the most affected domains were ocular, oral, and malignancy. Damage accrual was substantially increased in the malignancy domain. Additional studies with larger sample sizes and longer follow-up periods are needed in order to explore the applicability of these scores in routine practice (9). Furthermore, there are no comparative studies regarding the performance of both scores in the same population nor establishing a correlation between damage accrual, lymphoma development and mortality.

In this study, we aimed to establish whether damage and its kinetics, determined by SSDDI and SSDI, relate to mortality and lymphoma development in pSjD.

Methods

Patients

This is a single-centre open study that includes all consecutive patients with pSjD, followed up long term in the Rheumatology Department, University College London Hospital from January 1986 until February 2023. A substantial portion of the data was collected retrospectively, while the remaining data were obtained prospectively. All patients fulfilled the European Alliance of Associations for Rheumatology (EULAR) classification criteria (2016) for pSjD (11). Patients with associated SD, those under 18-year-old, and those whose diagnosis date was impossible to determine accurately were excluded.

Data collection and definitions

Demographic, clinical, laboratory, and therapeutic characterisation was carried out using electronic and paper files data. Data were collected from hospital electronic and paper records. Clinical manifestations were confirmed according to established criteria for each manifestation, using all available laboratory, imaging and/or histopathologic

Competing interests: D.A. Isenberg has received consultancies from Astra Zeneca, Viatris, Autolus, Novartis and Servier. All other authors have declared no competing interests.

Table I. Comparison of characteristics of patients with and without damage.

	SSDDI			SSDI		
	Damage (n=165)	No damage (n=43)	p-value	Damage (n=177)	No damage (n=31)	p-value
Age at diagnosis (years)	51.1 ± 14	45.5 ± 17.4	0.03	50.0 ± 14.7	49.7 ± 16.2	0.93
Age at disease onset (years)	46.8 ± 13.6	40.8 ± 18.7	0.07	45.6 ± 14.8	45.4 ± 16.4	0.96
Female	153 (92.7)	42 (97.7)	0.31	165 (93.2)	30 (96.8)	0.70
Ethnicity						
White	108 (70.1)	21 (52.5)	0.10	107 (65.6)	22 (71.0)	0.60
African-American	11 (7.1)	5 (12.5)		15 (9.2)	1 (3.2)	
Afro-Caribbean	5 (3.3)	0		3 (1.8)	2 (6.5)	
Asian	16 (10.4)	10 (25)		22 (13.5)	4 (12.9)	
Mixed	3 (2.0)	1 (2.5)		4 (2.5)	0	
Other	11 (7.1)	3 (7.5)		12 (7.4)	2 (6.5)	
Antibodies profile – positivity						
ANA	126 (82.4)	35 (92.1)	0.21	137 (83.5)	24 (88.9)	0.58
Anti-SSA/Ro	109 (71.7)	32 (78.1)	0.55	120 (73.2)	21 (72.4)	0.93
Anti-SSB/La	64 (42.1)	17 (41.5)	0.94	70 (42.7)	11 (37.9)	0.63
Anti-RNP	6 (4.0)	2 (5)	0.67	8 (4.9)	0	NA
Rheumatoid factor	92 (70.2)	20 (66.7)	0.83	99 (72.3)	13 (54.2)	0.08
Treatment (ever)						
Hydroxychloroquine	112 (68.3)	25 (59.5)	0.36	118 (67.4)	19 (61.3)	0.51
Methotrexate	9 (5.5)	2 (4.8)	0.85	10 (5.7)	1 (3.2)	1
Azathioprine	9 (5.5)	2 (4.76)	0.85	1 (3.2)	3 (9.7)	0.22
Sulfasalazine	8 (4.9)	1 (2.4)	0.69	8 (4.6)	1 (3.2)	0.74
Mycophenolate of mofetil	8 (4.9)	1 (2.3)	0.69	7 (4.0)	2 (6.5)	0.63
Cyclophosphamide	8 (4.9)	0	NA	8 (4.6)	0	NA
Rituximab	15 (9.2)	0	NA	13 (7.4)	2 (6.5)	0.86
Steroids (any dose)	66 (40.2)	13 (31.0)	0.27	71 (40.6)	8 (25.8)	0.12
High dose of steroids (>6mg)	61 (38.6)	10 (25)	0.11	65 (38.7)	6 (20)	0.06
Death	29 (20.7)	3 (7.9)	0.07	30 (19.9)	2 (7.4)	0.12
Time to death (years)	22 (14-27)	13 (9-30)	0.56	21.5 (12-27)	21.5 (13-30)	0.82

Continuous values shown in mean ± standard deviation or median and interquartile range if not normally distributed. Proportions reported in absolute number and percentage.

studies when applicable. Disease onset referred to the time the first symptom related to pSjD was noted and was distinguished from the diagnosis date. In our institution patients are requested to self-nominate the ethnic group they belong to. We have thus used the categories recorded in the hospital notes. SSDDI and SSDI scores were assessed annually from the time of diagnosis. Events lasting at least 6 months or resulting in permanent loss of organ function were deemed to be damage. The definitions of each event are in accordance with those listed in the original articles (7, 8). Early damage was considered if it occurred in the first year after diagnosis, while early damage increase was assumed when there was an increase of at least one point in damage in the first 5 years. A high dose of steroids was considered to be a dose above 6mg/day, based on previous studies carried out in patients with systemic lupus erythematosus, in which damage was found develop in those

taking steroid doses above 6mg/day (12). Any dose of intravenous methylprednisolone was considered high-dose steroid therapy.

Data shown in this study has been fully anonymised. It is considered to be an audit and thus not requiring formal ethical committee approval.

Statistical analysis

Statistical analysis was performed using STATA software (version 16.0). Categorical variables were expressed in number (%). Continuous variables were expressed as mean ± standard deviation, or median (interquartile range) after checking for normality using the Kolmogorov-Smirnov test. Categorical and continuous variables were compared using Chi-square and Student's t test or Mann-Whitney U test when appropriate. SSDDI and SSDI were compared according to domains using two sample test of proportions. Multivariate Cox regression analyses were performed to investigate signifi-

cant covariates related to mortality and the occurrence of lymphoma, such as established risk factors like positive rheumatoid factor and cryoglobulinaemia. Survival was analysed through the Kaplan-Meier method. A two-sided *p*-value <0.05 was considered statistically significant.

Results

Demographic and clinical characterisation

We identified 208 patients with pSjD followed for a mean of 14.1±9.2 years. Most patients were female (93.8%) and white (62.0%). The mean age at disease onset and at diagnosis was 45.6±15.0 years and 49.9±14.9 years, respectively. Damage (SSDDI and SSDI ≥1) was observed in 165 (79.3%) and 177 (85.1%) patients, assessed by the SSDI and SSDI scores, respectively (Supplementary Table S1). Demographic and clinical features were similarly distributed between patients with and without damage (Table I), except for

Table II. Comparison of affected domains using SSDDI and SSDI scores.

Domains	SSDDI score				SSDI score				<i>p</i> -value*
	Affected patients	Mean ± SD	Median (IQR)	Min-max	Affected patients	Mean ± SD	Median (IQR)	Min-max	
Ocular	109 (52.4)	0.7 ± 0.7	1 (0-1)	0-2	23 (11.1)	0.1 ± 0.3	0	0-1	< 0.001
Oral	70 (33.7)	0.4 ± 0.5	0 (0-1)	0-2	126 (60.6)	0.9 ± 0.9	0 (0-1)	0-3	< 0.001
Neurologic	75 (36.1)	0.6 ± 0.9	0 (0-1)	0-3	76 (36.5)	0.5 ± 0.7	0 (0-1)	0-2	0.92
Renal	34 (16.4)	0.3 ± 0.7	0 (0-0)	0-2	33 (15.9)	0.2 ± 0.4	0	0-1	0.89
Pulmonary	14 (6.7)	0.1 ± 0.5	0 (0-0)	0-2	16 (7.7)	0.1 ± 0.3	0	0-1	0.71
Cardiovascular	NA	14 (6.7)	0.1 ± 0.3	0	0-1	NA			
Gastrointestinal	NA	0	0	0	0	NA			
Musculoskeletal	NA	14 (6.7)	0.1 ± 0.3	0	0-1	NA			
Endocrine	NA	26 (12.5)	0.1 ± 0.3	0	0-1	NA			
Malignancy	18 (8.7)	0.4 ± 1.4	0 (0-0)	0-5	45 (21.6)	0.3 ± 0.7	0	0-3	<0.001

Continuous values shown in mean ± standard deviation or median and interquartile range if not normally distributed. Proportions reported in absolute number and percentage.

**p*-value refers to two sample test of proportions comparing affected patients in each domain.

Table III. Comparison of damage using SSDDI and SSDI scores.

Damage	SSDDI score			SSDI score		
	Dead (n = 32, 18.0)	Alive (n = 146, 82.1)	<i>p</i> -value	Dead (n = 32, 18.0)	Alive (n = 146, 82.1)	<i>p</i> -value
Early damage	6 (18.8)	45 (30.8)	0.20	7 (21.9)	60 (41.1)	0.05
Early damage increase	10 (33.3)	49 (37.7)	0.83	11 (36.7)	53 (40.8)	0.84
Early damage variation	0.5 ± 0.7	0.7 ± 1.3	0.38	0.5 ± 0.7	0.6 ± 0.9	0.54
Damage variation	3.5 ± 2.9	1.6 ± 1.9	< 0.001	3.0 ± 2.0	1.4 ± 1.5	< 0.001
Final damage score	3.8 ± 2.8	2.2 ± 2.2	< 0.001	3.3 ± 2.1	1.9 ± 1.6	< 0.001

Continuous values shown in mean ± standard deviation or median. Proportions reported in absolute number and percentage.

age at diagnosis, which was significantly higher in patients with damage as measured by the SSDDI (51.1±14.0 vs. 45.5±17.4 years; *p*=0.03) but not by the SSDI.

Damage acquisition

Ocular (52.4%), oral (33.7%) and neurological (36.1%) were the domains in which damage was most frequently recorded, when using the SSDDI score, while oral (60.6%), neurological (36.5%) and malignancy domains (21.6%) affectation were more prevalent when using the SSDI score (Table II). Ocular domain impairment was more prevalent using the SSDDI than the SSDI (52.4% vs. 11.1%). Compared to the SSDDI, the prevalence of impairment in the oral domain (33.7% vs. 60.6%) and malignancy (8.7% vs. 21.6%) were significantly higher when using the SSDI. Both scores identified similarly neurological, renal, and pulmonary damage (Table II). Damage acquisition in each subdomain is repre-

sented on Supplementary Table S2.

Damage distribution was also characterised considering glandular manifestations, defined by oral and/or ocular affection exclusively, and extra-glandular manifestations (Supplementary Table S2). In the first year after diagnosis, 45 (21.6%) patients acquired at least one point in the glandular damage domain, while 31 (14.9%) patients had extra-glandular damage, according to the SSDDI score. Similar results were obtained when applying the SSDI score regarding the presence of glandular damage (56 patients; 26.9%) and extra-glandular damage (33 patients; 15.9%). Glandular manifestations were significantly higher than extra-glandular manifestations in the first year of follow-up, according to the SSDI, while this difference was only visible at the end of follow-up when the SSDI score was applied. Non-statistically significant differences were detectable in glandular or extra-glandular features regardless of the score used.

Mortality and damage

Thirty-two patients (18.0%) died. Causes of death included infections (25.0%), cardiovascular events (9.4%), lymphoma (6.3%), and non-haematological cancer (3.1%). No information regarding the cause of death was available in 18 patients. However, the average age of these patients was 78.94±8.48 years, suggesting that many are likely to have died from natural causes. Except for age at diagnosis, which was significantly higher in deceased patients compared to those who remain alive (59.2±11.1 vs. 45.8±13.9 years, *p*<0.001), the remaining demographic features were similarly distributed between groups (Supplementary Table S3). The prevalence of anti-SSA/Ro antibody positivity was higher in surviving patients compared to those who died (84.9% vs. 48.0%, *p*<0.001). Deceased patients had higher cumulative SSDDI (3.8±2.8 vs. 2.2±2.2; *p*<0.001) and SSDI (3.3±2.1 vs. 1.9±1.6; *p*<0.001) compared to the sur-

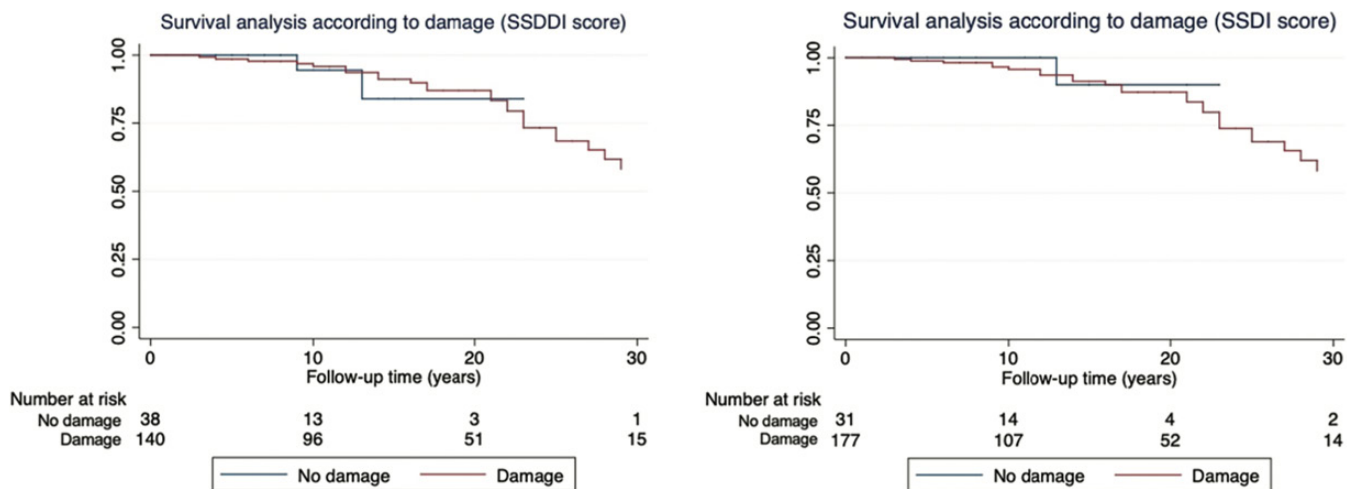


Fig. 1. Survival analysis according to damage (SSDDI and SSDI scores).

viving patients (Table III). The proportion of patients with early damage and early damage increase was similar in deceased and surviving patients, using both damage scores. Age at diagnosis (per one-unit increase HR 1.1, 95% CI 1.1-1.2) and age at symptoms onset (per one-unit increase HR 1.1, 95% CI 1.0-1.2) predicted mortality. However, neither damage (Figure 1), early damage (SSDDI: HR 0.6, 95% CI 0.2-1.7; SSDI: HR 0.8, 95% CI 0.2-1.7), early damage increase (SSDDI: HR 2.1, 95% CI 0.7-6.2; SSDI: HR 2.6, 95% CI 0.9-7.9), early damage variation (SSDDI: per one-unit increase HR 1.3, 95% CI 0.8-2.1; SSDI: per one-unit increase HR 1.7, 95% CI 0.9-3.0), total damage variation using the SSDI score (per one-unit increase HR 1.2, 95% CI 0.9-1.7) or final damage score (SSDDI: per one unit increase HR 1.2, 95% CI 0.9-1.5; SSDI: per one-unit increase HR 1.1, 95% CI 0.8-1.5) using either scores, predicted death. Only total damage variation using the SSDDI score retained statistical significance when accounting for relevant confounding factors (per one-unit increase HR 1.2, 95% CI 1.1-1.5).

Lymphoma development and damage

Seventeen patients (8.2%) developed lymphoma. Of these, the majority were mucosa-associated lymphoid tissue (MALT) lymphomas (58.8%), followed by other non-Hodgkin lymphomas (11.8%) and Hodgkin lymphoma (5.9%). In four patients (23.5%), the

Table IV. Comparison of characteristics of lymphoma and non-lymphoma patients.

	Lymphoma (n=17, 8.2)	Non-lymphoma (n=191, 91.8)	p-value
Female	16 (94.1)	179 (93.7)	0.95
Ethnicity			0.87
White	11 (64.7)	118 (66.7)	
African-American	1 (5.9)	15 (8.5)	
Afro-Caribbean	0	5 (2.8)	
Asian	3 (17.7)	23 (13.0)	
Mixed	0	4 (2.3)	
Other	2 (11.8)	12 (6.8)	
Age at diagnosis	46.1 ± 13.3	50.3 ± 15.0	0.26
Age at symptoms onset	46.5 ± 13.0	45.5 ± 15.2	0.84
Antibodies profile – positivity			
ANA	14 (93.3)	147 (83.5)	0.47
Anti-SSA/Ro	11 (78.6)	130 (72.6)	0.76
Anti-SSB/La	6 (42.9)	75 (41.9)	0.94
Anti-RNP	1 (7.1)	7 (3.9)	0.46
Rheumatoid factor	9 (81.8)	103 (68.7)	0.51
Treatment (ever)			
Hydroxychloroquine	9 (56.3)	128 (67.4)	0.41
Methotrexate	1 (6.3)	10 (5.3)	0.60
Azathioprine	2 (12.5)	9 (4.7)	0.21
Sulfasalazine	0	9 (4.7)	NA
Mycophenolate of mofetil	0	9 (4.7)	NA
Cyclophosphamide	5 (31.3)	3 (1.6)	< 0.001
Rituximab	9 (56.3)	6 (3.2)	< 0.001
Steroids (any dose)	11 (68.8)	68 (35.8)	0.01
High dose of steroids (>6mg)	12 (75)	59 (32.4)	0.002
Follow-up period (years)	10 (IQR 7-23)	12 (IQR 7-20)	0.94
Mortality	5 (33.3)	27 (16.6)	0.15

Continuous values shown in mean ± standard deviation or median and interquartile range if not normally distributed. Proportions reported in absolute number and percentage.

lymphoma subtype could not be determined. The diagnosis of lymphoma occurred at an average of 7.4 ± 7.0 years after pSjD diagnosis. Lymphomas diagnosed before pSjD diagnosis were excluded. Regarding sex, ethnicity, age at diagnosis and at disease onset, and serological profile did not differ between patients with or without lymphoma

(Table IV). Five patients in the lymphoma group died (33.3%), two of them due to this condition. A higher proportion of patients with cryoglobulinaemia was observed in the lymphoma group (17.7% vs 0.5%; $p < 0.002$). The development of glandular and extra-glandular damage was similar in patients with and without lymphoma,

Table V. Comparison of damage in lymphoma and non-lymphoma patients using SSDDI and SSDI scores.

Damage	SSDDI score			SSDI score		
	Lymphoma	No lymphoma	<i>p</i> -value	Lymphoma	No lymphoma	<i>p</i> -value
Early damage	5 (29.4)	60 (31.4)	0.87	6 (35.3)	78 (38.2)	0.81
Early damage increase	11 (68.8)	58 (34.9)	0.01	10 (62.5)	67 (40.4)	0.11
Early damage variation	1.9 ± 2.5	0.5 ± 0.9	< 0.001	1.2 ± 1.3	0.6 ± 0.8	0.005
Damage variation	5.9 ± 3.5	1.5 ± 1.6	< 0.001	3.4 ± 2.2	1.5 ± 1.5	< 0.001
Final damage score	7.7 ± 2.0	2.0 ± 1.8	< 0.001	4.0 ± 2.2	2.0 ± 1.6	< 0.001

Continuous values shown in mean ± standard deviation or median and interquartile range if not normally distributed. Proportions reported in absolute number and percentage.

regardless the score used (Supplementary Table S4).

Patients with lymphoma had significantly higher cumulative SSDDI (7.7±2.0 vs. 2.0±1.8; $p<0.001$) and SSDI (4.0±2.2 vs. 2.0±1.6; $p<0.001$) scores compared to patients without lymphoma. The prevalence of early damage was similar in patients with and without lymphoma (Table V). When performing multivariate Cox analysis, early damage did not predict lymphoma using either score (SSDDI: HR 0.8, 95% CI 0.2-2.9; SSDI: HR 0.9, 95% CI 0.3-3.1). However, early damage increase predicted the development of lymphoma using the SSDDI (HR 14.5, 95% CI 1.8-115) and the SSDI score (HR 12.8, 95% CI 1.5-108.1). Early damage variation (SSDDI: per one unit increase HR 1.8, 95% CI 1.4-2.2; SSDI: per one-unit increase HR 2.5, 95% CI 1.6-4.0) and the cumulative score (SSDDI: per one unit increase HR 2.0, 95% CI 1.5-2.7; SSDI: per one-unit increase HR 1.5, 95% CI 1.0-2.3) were predictors of lymphoma when controlling for relevant confounding factors. Total damage variation using the SSDDI score also predicted lymphoma (per one-unit increase HR 1.6, 95% CI 1.3-1.9) but only revealed a non-significant trend for increased risk when using the SSDI score (per one-unit increase HR 1.5, 95% CI 0.9-2.2).

Discussion

In this study we have characterised and compared for the first time the damage accrual as measured by the SSDDI and SSDI scores in the same group of patients with pSjD. We found that damage accrual, especially in the first five years, seems to be associated with lymphoma development but not mortality, in this population.

Damage reflects an irreversible structural or functional impairment resulting from persistent disease activity and/or treatment side effects (13). Previous studies reported an association between damage and mortality in systemic lupus erythematosus (14). However, few studies investigated damage acquisition, its kinetics and long-term outcomes in pSjD (15). In this study, the majority (>75%) of the patients developed damage, regardless of the score used. In an earlier study of this group of pSjD patients (10) damage was reported in less than half of 66 patients with pSjD, using the SSDI score. This discrepancy might be explained by the longer follow-up in our study (14.1±9.2 years compared to a maximum of 10 years in the previous study). However, the cumulative and evolving damage observed in our cohort is consistent with previous studies, demonstrating a progressive increase in damage over time, particularly from the fifth year of disease onward, and the presence of distinct patterns of damage distribution across domains (16).

Comparing both scores, despite similar values for damage acquisition, SSDDI and SSDI differ in terms of the number of domains, the number of items included in each domain, and the weight attributed to them. The SSDI score is more complex and encompasses more domains and items, and has better sensitivity, particularly for oral (60.6%), neurological (36.5%) and malignancy (21.6%). Neurological damage was substantially different from previous studies, which only reported 3.3%. Finally, malignancy was also higher than reported (10%) in our earlier study (10). This domain includes NHL, other haematologic malignancies, and solid organ malignancies. These differences might be due to a longer follow-up period, and the fact that part of this damage occurred after 10 years, which corresponds to the maximum follow-up period of the study previously reported. Damage reported in the oral domain is also very different from what was reported previously, not only because of the longer follow-up period but also due to the larger amount of available data, allowing us to score not only glandular swelling but also the other items in the domain. When the SSDDI score was applied, oral and neurological domains were also the most affected. However, the ocular domain was the most prevalent in this score. This difference can be explained by the inclusion of more frequent findings such as cataracts, corneal ulcers, and chronic blepharitis in the score. In addition, the cut-off considered for the Schirmer test is less strict (<5 mm vs. 0 mm).

Damage acquisition, including early damage, did not predict mortality, as reported previously (10). This may be due to the small number of events, hampering the identification of risk factors. In addition, most of the damage occurred in domains that confer significant loss of quality of life but not increased mortality, such as ocular, oral and neurologic domains. Furthermore, most haematological neoplasms related to this disease have a good prognosis (17). Although there was no causal relationship identified, it was found that deceased individuals had greater cumulative damage, which emphasises the need to quantify and prevent it earlier. Age at presentation and diagnosis predicted mortality, which is in line with

(10). This domain includes NHL, other haematologic malignancies, and solid organ malignancies. These differences might be due to a longer follow-up period, and the fact that part of this damage occurred after 10 years, which corresponds to the maximum follow-up period of the study previously reported. Damage reported in the oral domain is also very different from what was reported previously, not only because of the longer follow-up period but also due to the larger amount of available data, allowing us to score not only glandular swelling but also the other items in the domain. When the SSDDI score was applied, oral and neurological domains were also the most affected. However, the ocular domain was the most prevalent in this score. This difference can be explained by the inclusion of more frequent findings such as cataracts, corneal ulcers, and chronic blepharitis in the score. In addition, the cut-off considered for the Schirmer test is less strict (<5 mm vs. 0 mm).

Damage acquisition, including early damage, did not predict mortality, as reported previously (10). This may be due to the small number of events, hampering the identification of risk factors. In addition, most of the damage occurred in domains that confer significant loss of quality of life but not increased mortality, such as ocular, oral and neurologic domains. Furthermore, most haematological neoplasms related to this disease have a good prognosis (17). Although there was no causal relationship identified, it was found that deceased individuals had greater cumulative damage, which emphasises the need to quantify and prevent it earlier. Age at presentation and diagnosis predicted mortality, which is in line with

previous studies (18, 19). Surprisingly, the prevalence of anti-SSA/Ro positivity was higher in survivors despite previous reports which did not observe this (18-20). Deceased patients were older at both disease onset and diagnosis. These patients typically show a lower frequency of anti-SSA positivity, as reported in previous studies (21, 22). Thus, the inverse association observed in our cohort may reflect a seronegative phenotype rather than suggesting any protective effect of anti-SSA antibodies. Moreover, seronegative patients are often diagnosed later in the disease course and may carry a greater burden of comorbidities, both of which could contribute to their increased mortality risk.

We identified, for the first time, that damage accrual, particularly in the first years, as a possible predictor of lymphoma in pSjD patients. Even though this finding needs confirmation, it shows the importance of early damage assessment as a means of identifying those patients who might benefit from intensification of treatment. We speculate that individuals with early damage have chronic activation of the immune system and increased oxidative stress from an early stage of the disease, promoting chronic inflammation and favouring the development of lymphoma in the future. Although these patients may have higher disease activity, to assess this was beyond the scope of the present study. Surprisingly, there were no differences between glandular and extra-glandular damage regarding lymphoma development. Considering that exocrine glands are the main sites for the formation of ectopic germinal centres, it would be expected that glandular damage would be a predictor of lymphoma in these patients (20). No serological differences were identified between individuals with and without lymphoma, contrary to previous studies (23, 24). This is possibly due to the low number of events reported.

This study does have some limitations. It is a single-centre study; thus, extrapolation of results cannot be guaranteed. In addition, there are some missing data notably in respect of the causes of mortality. Given the fact that the median age of the population included is 50 years, other factors can impact and contribute to damage acquisition, such as cardiovascular risk factors and other comorbidities common in this range.

To assess this was beyond the scope of this study. However, being a single centre study also allows for greater continuity of the data acquisition with one of the authors (DAI) overseeing the clinic in which these patients were seen throughout the >30 years of follow-up in some cases. Finally, despite controlling in Cox regression models, assessment of cryoglobulinaemia as a predictor of mortality or lymphoma may be biased by its presence as an item in SSDI scores.

In conclusion, damage accrual, particularly in the first five years of the disease, seems to be associated with lymphoma development in patients with pSjD. However, an association with mortality was not demonstrated in this study. Damage scores should be part of the pSjD patients' routine evaluation.

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