Systemic manifestations of primary Sjögren's syndrome out of the ESSDAI classification: prevalence and clinical relevance in a large international, multi-ethnic cohort of patients

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Competing interests: see page S-104.

ABSTRACT

Objective. *To analyse the frequency and characterise the systemic presentation of primary Sjögren's syndrome (SS) out of the ESSDAI classification in a large international, multi-ethnic cohort of patients.*

Methods. *The Big Data Sjögren Project Consortium is an international, multicentre registry based on worldwide data-sharing and cooperative merging of pre-existing clinical SS databases from leading centres in clinical research in SS from the five continents. A list of 26 organ-by-organ systemic features not currently included in the ESSDAI classification was defined according to previous studies; these features were retrospectively recorded.*

Results. *Information about non-ESSDAI features was available in 6331 patients [5,917 female, mean age at diagnosis 52 years, mainly White (86.3%)]. A total of 1641 (26%) patients had at least one of the ESSDAI systemic features. Cardiovascular manifestations were the most frequent organ-specific group of non-ESSDAI features reported in our patients (17% of the total cohort), with Raynaud's phenomenon being reported in 15%. Patients with systemic disease due to non-ESSDAI features had a lower frequency of dry mouth (90.7% vs. 94.1%, p<0.001) and positive minor salivary gland biopsy (86.7% vs. 89%, p=0.033), a higher frequency of anti-Ro/SSA (74.7% vs. 68.7%, p<0.001), anti-La/SSB antibodies (44.5% vs. 40.4%, p=0.004), ANA (82.7% vs. 79.5%, p=0.006), low C3 levels (17.4% vs. 9.7%, p<0.001), low C4 levels (14.4% vs. 9.6%, p<0.001), and positive serum cryoglobulins (8.6% vs. 5.5%, p=0.001). Systemic activity measured by the ESSDAI, clinESSDAI and DAS was higher in patients with systemic disease out of the ESSDAI in comparison with those without these features (p<0.001 for all comparisons).*

Conclusion. *More than a quarter of patients with primary SS may have systemic manifestations not currently included in the ESSDAI classification, with a wide variety of cardiovascular, digestive, pulmonary, neurological, ocular, ENT (ear, nose, and throat), cutaneous and urological features that increase the scope of the systemic phenotype of the disease. However, the individual frequency of each of these non-ESSDAI features was very low, except for Raynaud's phenomenon.*

Introduction

Primary Sjögren's syndrome (SS) is a systemic autoimmune disease in which the immune system targets the exocrine glands (1). The disease affects women in more than 95% of reported cases, with a frequency ranging between 0.01 and 0.72% (2). The key clinical presentation of primary SjS is sicca syndrome, reported by more than 95% at the time of diagnosis (3), although patients may also develop a wide variety of systemic manifestations, which may even be the presenting manifestation (4).

Over the decades, systemic SS features have been heterogeneously defined and classified; this has resulted in lack of clarity and consensus about the frequency and clinical presentation of systemic SS. Together with a lack of a consensual, international point of view, several groups included as systemic manifestations of the disease some organ-specific features (hepatic, thyroid, pancreatic) that are currently considered out of the aetiopathogenetic basis that characterises the disease, either because they are well-defined organ-specific diseases (autoimmune thyroiditis, primary biliary colangitis or autoimmune hepatitis) coexisting with primary SS, associated viral infections (such as chronic hepatitis C virus [HCV] infection for liver involvement), closer to other systemic autoimmune disease [SAD] (such as serositis or Raynaud's phenomenon [RP]), or even traditionally considered as forming part of the disease (pancreatic involvement), but with a practical inexistence in the current daily practice.

In 2010 a EULAR (European League Against Rheumatism) task force involving a collaboration of experts identified through their involvement in the primary SS field developed the EULAR-SS disease activity score (ESSDAI) (5), an index developed using physician global assessment (PhGA) of disease activity as an external criterion. The experts agreed on the inclusion of 11 clinical domains (constitutional, lymphadenopathy, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral nervous system, central nervous system, haematological) excluding other features such as haepatic (considered to result from damage) or pancreatic. The definition of the different activity levels (items) of each domain was obtained by consensus after discussion during meetings of the steering committee and experts. The development of the ESSDAI has represented a step forward in the evaluation of systemic SS allowing a homogeneous evaluation of systemic disease in large series of patients (6-9), and recent studies have linked higher ESSDAI scores with poor outcomes in multicentre registries from European countries (10-13), making the baseline ESSDAI score a solid prognostic marker.

However, several systemic features, out of the ESSDAI classification, have been increasingly being reported in patients with primary SS; these features may be different from those included in some already-defined organ-specific domains (some cutaneous, pulmonary or neurological features) or may be features involving other organs (cardiovascular, autonomic nervous system, urologic, ocular or ENT [ear, nose, and throat]) (14). Both the prevalence and the clinical relevance of these systemic features not included in the ESSDAI is currently unknown.

The objective of this study was to analyse the frequency and characterise the systemic manifestations of primary SS out of the ESSDAI classification in a large international, multi-ethnic cohort of patients.

Methods

Patients

The Big Data Sjögren Project Consortium is an international, multicentre registry designed in 2014 to take a "high-definition" picture of the main features of primary SS using worldwide data-sharing cooperative merging of pre-existing clinical SS databases from leading centres in clinical research in SS from the five continents (see reference 3 for additional methodological details). The centres share a harmonised data infrastructure and conduct cooperative online efforts in order to refine already-collected data in each centre, under the coordination of a statistical researcher (NAD). Inclusion criteria were fulfilment of the 2002 classification criteria (15). Exclusion criteria for considering SS as a primary disease were chronic HCV/HIV infection, previous lymphoproliferative processes, and associated systemic autoimmune diseases. Diagnostic tests for SS (ocular tests, oral tests and salivary gland biopsy) were carried out according to the recommendations of the European Community Study Group (16). The study was approved by the Ethics Committee of the Coordinating Centre (Hospital Clinic, Barcelona, Spain, registry HCB/2015/0869).

Definition of variables

Disease diagnosis was defined as the time when the attending physician confirmed fulfilment of the 2002 criteria. The main disease features at this time were retrospectively collected and analysed. The following clinical variables were selected for harmonisation and further refinement: age, gender, ethnicity, country of residence, fulfilment of the 2002 criteria items, antinuclear antibodies, rheumatoid factor (RF), C3 and C4 levels, cryoglobulins. The epidemiological variables included in this study were age at diagnosis, gender and ethnicity according to Food and Drug Administration (FDA) definitions (17). Systemic involvement at diagnosis was retrospectively classified and scored according to the ESSDAI (5), which evaluates 12 domains or organ systems, and the clinESSDAI (18), which evaluates the same domains but excluding the last (biological) domain. Each domain is divided into 3-4 levels according to the degree of activity and scored as 0 (no activity), 1 (low activity), 2 (moderate activity) or 3 (high activity) (19). Disease activity states (DAS) were calculated as: no activity (global score = 0), low activity (global score 1-4), moderate activity (global score 5-13) and high activity (global score ≥14) (20).

A list of 26 organ-by-organ systemic features not currently included in the ESSDAI classification was defined according to previous studies (14); these features were retrospectively recorded. By January 2019, the participant centres had included 11,420 valid patients from 24 countries; recorded information on these features was available in 6331 patients.

Statistical analysis

Descriptive data are presented as mean and standard deviation (SD) for continuous variables and numbers and percentages (%) for categorical variables. The Chi-square test was used to study systemic manifestations of primary SS out of the ESSDAI classification at diagnosis according to the gender, ethnicity, diagnostic tests for SS, immunological markers and systemic involvement. The t-test was used to compare the mean

age at diagnosis, ESSDAI and clinESSDAI scores. The Odds Ratios (ORs) and their 95% confidence intervals (CIs) were obtained in the logistic regression analysis considering patients scored as active (at least one systemic manifestation of primary SS out of the ESSDAI classification) at diagnosis time according to the dichotomised variables at diagnosis (gender, diagnostic tests for SS, immunological markers and systemic involvement). Bubble charts were used to compare the frequency between systemic manifestations of primary SS out of the ESSDAI classification at diagnosis and systemic activity recorded in the ESSDAI organ domains at diagnosis. To handle missing data due to non-evaluated features, "available case analysis" was assumed. All significance tests were two-tailed and values of p <0.05 were considered significant. p-values were adjusted for multiple comparisons using the false discovery rate (FDR) correction. All analyses were conducted using the R v. 3.5.0 for Windows statistical software package (https://www.R-project.org/).

Results

The baseline characteristics of the cohort analysed are summarised in Supplementary Table 1, and included 5,917 (93.5%) women with a mean age at diagnosis of primary SS of 52.4 (SD 14.1) years. The frequencies of fulfilment of the 2002 classification criteria items were 92.4% for dry eye (item I), 93.7% for dry mouth (item II), 83% for abnormal ocular tests (item III), 81.6% for positive minor salivary gland biopsy (item IV), 78% for abnormal oral diagnostic tests (item V) and 75.8% for positive anti-Ro/La antibodies (item VI). The frequency of other immunological markers at diagnosis was: positive antinuclear antibody (ANA) in 79.1% of patients, positive RF in 47.9, low C3 levels in 13.4%, low C4 levels in 14.6% and positive serum cryoglobulins in 7% of patients. The mean total ESSDAI score at diagnosis of the entire cohort was 6.1 (SD 7.5); 81.8% of patients had systemic activity (global ESSDAI score ≥1) at diagnosis (Supplementary Table 1). The domains with the highest frequency of active patients included the biological (51%), articular (37.7%), haematological (22.4%), glandular (21.4%) and pulmonary (10.4%) domains.

A total of 1641 (26%) of 6331 patients presented at least one of the ESSDAI systemic features listed in Annex 1; among them, there were 359 (22%) patients who presented two or more of these features. Table I summarises the frequency of each individual non-ESSDAI systemic features. The most frequent organs involved included cardiovascular in 1079 (17%) patients, digestive in 390 (6.2%), pulmonary in 145 (2.3%), neurological in 110 (1.7%), ocular in 97 (1.5%), ENT in 80 (1.3%), cutaneous in 55 (0.9%) and urological features in 43 (0.7%) patients.

Table II compared the main features at diagnosis of patients according to the presence or absence of at least one non-ESSDAI systemic feature. Patients with systemic disease out of the ESSDAI were predominantly younger (51.7 *vs*. 52.6, p=0.018), classified as White (86.3% *vs*. 75.9%, p<0.001), had a lower frequency of dry mouth (90.7% *vs*. 94.1%, p<0.001) and positive minor salivary gland biopsy (86.7% *vs*. 89%, p=0.033), a higher frequency of anti-Ro/SSA (74.7% *vs*. 68.7%, p<0.001), anti-La/SSB antibodies (44.5% *vs*. 40.4%, p=0.004), ANA (82.7% *vs*. 79.5%, p=0.006), low C3 levels (17.4% *vs*. 9.7%, p<0.001), low C4 levels (14.4% *vs*. 9.6%, p<0.001), and positive serum cryoglobulins (8.6% *vs*. 5.5%, p=0.001). Systemic activity at diagnosis was significantly higher in patients with systemic disease out of the ESSDAI in comparison with those without these features, including a higher mean ESSDAI (10.3 *vs*. 5.5, p<0.001), a higher mean ClinESSDAI score (10.8 *vs*. 5.7, p<0.001) and a high systemic activity (high-DAS) (27% *vs*. 11.3%, p<0.001). With respect to the organ-specific ESSDAI domains, patients with non-ESSDAI systemic disease had a higher frequency of activity in the constitutional (16% *vs*. 7.6%, p<0.001), lymphadenopathy (14.3% *vs*. 9.5%, p<0.001), glandular (31.8% *vs*. 22.6%, p<0.001), articular (47.7% *vs*. 39.2%, p<0.001), cutaneous (16.1% *vs*. 8.3%, p<0.001), pulmonary (19.6% *vs*. 8.9%, p<0.001), renal (9% *vs*. 3.7%, p<0.001), muscular (7.3% *vs*. 1.5%, p<0.001), peripheral nervous system (11.6% *vs*. 4.4%, p<0.001), central nervous system (3.2% *vs*. 1.4%, p<0.001), haematological (26.8% *vs*. 20.7%, p=<0.001) and biological (57.6% *vs*. 46.7%, p<0.001) domains.

Table I. Percentage of patients with systemic features out of the ESSDAI.

Patients with features out of ESSDAIn (%)	
*None	4690 (74.1%)
*1 feature	1282 (20.2%)
*2 features	284 (4.5%)
*3 or more features	75 (1.2%)
Cardiovascular features	**1079 (17%)**
Raynaud phenomenon	958 (15.1%)
Congenital heart block	29 (0.5%)
Pericarditis	46 (0.7%)
Myocarditis	2 (0%)
Valvular disease	94 (1.5%)
Pulmonary features	**145 (2.3%)**
Pleuritis	100 (1.6%)
Pulmonary arterial hypertension	52 (0.8%)
Digestive features	**390 (6.2%)**
Dysphagia	174 (2.7%)
Chronic gastritis	194 (3.1%)
Protein-losing enteropathy	1 (0%)
Acute pancreatitis	41 (0.6%)
Ocular features	**97 (1.5%)**
Uveitis	55 (0.9%)
Episcleritis	37 (0.6%)
Orbital pseudotumour	11 (0.2%)
Cutaneous features	**55 (0.9%)**
Erythema nodosum	23 (0.4%)
Panniculitis	10 (0.2%)
Amyloidosis	12 (0.2%)
Granuloma annulare	10 (0.2%)
ENT features	**80 (1.3%)**
Hearing loss	35 (0.6%)
Chondritis	2 (0%)
Laryngitis	10 (0.2%)
Sinusitis	34 (0.5%)
Neurological features	**110 (1.7%)**
Dysautonomia /autonomic dysfunction	28 (0.4%)
Small-fibre neuropathy	50 (0.8%)
Restless leg syndrome	36 (0.6%)
Urological features	**43 (0.7%)**
Interstitial cystitis	43 (0.7%)

Table III summarises the main epidemiological, immunological and systemic features of patients with active systemic disease out of ESSDAI grouped organ-by-organ. Some specific phenotypic patterns were identified. Patients with pulmonary manifestations not included in the ESSDAI classification showed the highest frequencies of positive Ro/La antibodies and activity in the non-neurological ESSDAI domains, while those with neurological manifestations not included in the ESSDAI classifica-

Table II. Epidemiological features, glandular involvement, systemic involvement and immunological profile in patients with primary Sjögren's syndrome with and without features out of the ESSDAI.

Variable	Patients with features out of ESSDAI (n=1641)	Patients without features out of ESSDAI (n=4690)	*p*-value	Adjusted *p*-value	OR [CI95%]
Gender (female)	1534/1641 (93.5)	4383/4690 (93.5)	1	1	1 [0.8-1.27]
Age at diagnosis	51.7 ± 13.3	52.6 ± 14.1	0.018	0.023	
Ethnicity			<0.001	<0.001	
White	1410/1634 (86.3)	3543/4668 (75.9)			
Asian	55/1634 (3.4)	445/4668 (9.5)			
Hispanic	126/1634 (7.7)	455/4668 (9.7)			
Black/African American	20/1634 (1.2)	70/4668 (1.5)			
Others	23/1634 (1.4)	155/4668 (3.3)			
Dry eye	1559/1641 (95)	4404/4690 (93.9)	0.114	0.132	1.23 [0.96-1.61]
Dry mouth	1489/1641 (90.7)	4413/4690 (94.1)	<0.001	<0.001	0.61 [0.5-0.76]
Abnormal ocular tests	1336/1530 (87.3)	3650/4251 (85.9)	0.169	0.187	1.13 [0.95-1.36]
Positive minor salivary gland biopsy	995/1148 (86.7)	3139/3525 (89)	0.033	0.039	0.8 [0.65-0.98]
Abnormal oral diagnostic tests	1034/1325 (78)	2808/3607 (77.8)	0.918	0.949	1.01 [0.87-1.18]
Anti-Ro antibodies	1212/1623 (74.7)	3175/4624 (68.7)	<0.001	<0.001	1.35 [1.18-1.53]
Anti-La antibodies	718/1613 (44.5)	1858/4602 (40.4)	0.004	0.006	1.18 [1.05-1.33]
ANA positive	1338/1618 (82.7)	3643/4582 (79.5)	0.006	0.008	1.23 [1.06-1.43]
RF positive	650/1484 (43.8)	1883/4160 (45.3)	0.346	0.37	0.94 [0.83-1.06]
C3 low	252/1448 (17.4)	383/3962 (9.7)	<0.001	<0.001	1.97 [1.65-2.35]
C4 low	209/1452 (14.4)	381/3984 (9.6)	<0.001	<0.001	1.59 [1.32-1.91]
Positive cryoglobulins	91/1053 (8.6)	122/2222 (5.5)	0.001	0.001	1.63 [1.21-2.18]
ESSDAI	10.3 ± 11.9	5.5 ± 6.3	<0.001	<0.001	
ClinESSDAI	10.8 ± 12.9	5.7 ± 6.9	<0.001	<0.001	
DAS			<0.001	<0.001	
Low	662/1559 (42.5)	2555/4359 (58.6)			
Moderate	476/1559 (30.5)	1311/4359 (30.1)			
High	421/1559 (27)	493/4359 (11.3)			
ESSDAI domains					
Constitutional	262/1637 (16)	348/4565 (7.6)	<0.001	<0.001	2.31 [1.94-2.75]
Lymphadenopathy	235/1641 (14.3)	436/4585 (9.5)	<0.001	<0.001	1.59 [1.34-1.89]
Glandular	520/1635 (31.8)	1029/4562 (22.6)	<0.001	<0.001	1.6 [1.41-1.82]
Articular	782/1638 (47.7)	1787/4564 (39.2)	<0.001	<0.001	1.42 [1.26-1.59]
Cutaneous	265/1641 (16.1)	379/4585 (8.3)	<0.001	<0.001	2.14 [1.8-2.54]
Pulmonary	322/1641 (19.6)	410/4585 (8.9)	<0.001	<0.001	2.49 [2.11-2.92]
Renal	147/1638 (9)	169/4564 (3.7)	<0.001	<0.001	2.56 [2.02-3.24]
Muscular	120/1638 (7.3)	67/4560 (1.5)	<0.001	<0.001	5.3 [3.87-7.3]
PNS	190/1635 (11.6)	200/4558 (4.4)	<0.001	<0.001	2.86 [2.32-3.54]
CNS	53/1635 (3.2)	63/4560 (1.4)	<0.001	<0.001	2.39 [1.62-3.52]
Haematological	438/1634 (26.8)	943/4562 (20.7)	<0.001	<0.001	1.41 [1.23-1.6]
Biological	904/1570 (57.6)	2059/4408 (46.7)	<0.001	<0.001	1.55 [1.38-1.74]

tion showed the highest rate of White patients involved and the highest frequencies of activity in the neurological ESSDAI domains, and those with ocular non-ESSDAI manifestations showing the highest frequency of active disease in the glandular ESSDAI domain.

Table IV summarises the main epidemiological, immunological and systemic features of the 10 non-ESSDAI features most frequently reported. Cardiopulmonary features clearly stood out among all features as those more closely linked to both Ro/La autoantibodies and systemic phenotype. Specifically, pleuritis and pulmonary arterial hypertension (PAH) were associated with the highest frequencies of anti-Ro (83 and 86%, respectively), anti-La (66 and 65%, respectively) and mean values of global ESSDAI scores (21.7 and 21.5, respectively), followed by valvular disease and pericarditis (75% and 83% for anti-Ro, 47 and 59% for anti-La, 17.4 and 14.2 for mean ESSDAI; respectively) (Fig. 1).

Discussion

This study reports, for the first time, that more than a quarter of patients with primary SS may have systemic manifestations not currently included in the ESSDAI classification, with a wide variety of cardiovascular, digestive, pulmonary, neurological, ocular, ENT, cutaneous and urological features that increase the scope of the systemic phenotype of the disease. However, the individual frequency of each of these non-ESSDAI features should be considered very low, except for RP (15%). There are only 4 other features with frequencies ranging between 1 and 3%, and for the remaining 21 features, the individual frequency was below the 1%. These findings underline the wide clinical phenotypic expression of systemic autoimmune diseases, but also the highly disease-specific design of the ESSDAI, that currently includes the most frequent systemic features of the disease. According to our results, the ESSDAI domain with the lowest frequency was the muscular domain, reported in 3% of patients, and only 3 out of the 26 non-ESSDAI features we analysed are above this frequency.

Table III. Organ-by-organ characterisation of patients with primary SS presenting with features out of the ESSDAI.

Variable	Cardiovascular (n=1079)	Digestive (n=390)	Pulmonary (n=145)	Neurological (n=110)	Ocular (n=97)	ENT (n=80)	Cutaneous (n=55)	Urological (n=43)
Gender (female)	1023/1079 (94.8)	371/390 (95.1)	125/145 (86.2)	100/110 (90.9)	85/97 (87.6)	70/80 (87.5)	54/55 (98.2)	41/43 (95.3)
Age at diagnosis	51.2 ± 13.8	52.5 ± 12.7	52.6 ± 13.1	55.1 ± 12.5	51.9 ± 11.2	53.9 ± 13.2	51.8 ± 11.3	55.4 ± 9.3
Ethnicity (white)	947/1074 (88.2)	329/387 (85)	132/144 (91.7)	102/110 (92.7)	87/97 (89.7)	54/80 (67.5)	43/55 (78.2)	35/42 (83.3)
Anti-Ro antibodies	831/1069 (77.7)	291/386 (75.4)	119/143 (83.2)	74/109 (67.9)	68/94 (72.3)	51/80 (63.7)	34/54 (63)	29/41 (70.7)
Anti-La antibodies	481/1064 (45.2)	183/383 (47.8)	92/143 (64.3)	46/109 (42.2)	44/92 (47.8)	32/79 (40.5)	17/53 (32.1)	21/40 (52.5)
ESSDAI	10.8 ± 12.4	12.5 ± 14.6	20.9 ± 19.2	15.5 ± 17.1	10.7 ± 11.8	5.6 ± 5.7	5 ± 5.6	10.9 ± 12.9
ClinESSDAI	11.4 ± 13.4	13 ± 15.8	22.7 ± 20.9	16.8 ± 18.3	11.2 ± 12.7	5.8 ± 6.1	5.5 ± 6	11.9 ± 13.6
ESSDAI domains								
Constitutional	181/1077 (16.8)	74/387 (19.1)	48/145 (33.1)	18/110 (16.4)	23/97 (23.7)	5/80 (6.2)	5/55 (9.1)	7/43 (16.3)
Lymphadenopathy	166/1079 (15.4)	43/390 (11)	29/145 (20)	14/110 (12.7)	18/97 (18.6)	9/80 (11.2)	7/55 (12.7)	3/43 (7)
Glandular	334/1078 (31)	147/388 (37.9)	63/145 (43.4)	34/110 (30.9)	41/94 (43.6)	16/80 (20)	8/55 (14.5)	13/43 (30.2)
Articular	532/1078 (49.4)	175/388 (45.1)	83/145 (57.2)	48/110 (43.6)	44/97 (45.4)	27/80 (33.8)	24/55 (43.6)	21/43 (48.8)
Cutaneous	203/1079 (18.8)	59/390 (15.1)	35/145 (24.1)	26/110 (23.6)	13/97 (13.4)	8/80 (10)	9/55 (16.4)	7/43 (16.3)
Pulmonary	215/1079 (19.9)	93/390 (23.8)	83/145 (57.2)	25/110 (22.7)	22/97 (22.7)	4/80 (5)	4/55 (7.3)	8/43 (18.6)
Renal	94/1078 (8.7)	49/388 (12.6)	42/145 (29)	15/110 (13.6)	7/97 (7.2)	4/80 (5)	1/55 (1.8)	9/43 (20.9)
Muscular	82/1078 (7.6)	41/388 (10.6)	20/145 (13.8)	14/110 (12.7)	10/97 (10.3)	1/80 (1.2)	0/55 (0)	4/43 (9.3)
PNS	137/1078 (12.7)	55/388 (14.2)	23/145 (15.9)	49/110 (44.5)	9/94 (9.6)	5/80 (6.2)	2/55 (3.6)	5/43 (11.6)
CNS	32/1078 (3)	17/388 (4.4)	9/145 (6.2)	16/110 (14.5)	3/94 (3.2)	5/80 (6.2)	1/55 (1.8)	1/43 (2.3)
Haematological	309/1075 (28.7)	108/389 (27.8)	54/144 (37.5)	31/110 (28.2)	31/97 (32)	20/77 (26)	8/55 (14.5)	9/43 (20.9)
Biological	623/1038 (60)	248/369 (67.2)	106/142 (74.6)	50/108 (46.3)	46/92 (50)	32/71 (45.1)	21/49 (42.9)	21/42 (50)

Table IV. Characterisation of the 10 most frequently reported out of the ESSDAI features in patients with primary SS.

Variable	Raynaud's phenomenon (n=958)	Chronic gastritis (n=194)	Dysphagia (n=174)	Pleuritis (n=100)	Small-fibre neuropathy (n=50)	Valvular disease (n=94)	Uveitis (n=55)	Pulmonary artery hypertension (n=52)	Pericarditis (n=46)	Interstitial cystitis (n=43)
Gender (female)	914/958 (95.4)	181/194 (93.3)	169/174 (97.1)	84/100 (84)	46/50 (92)	86/94 (91.5)	50/55 (90.9)	46/52 (88.5)	40/46 (87)	41/43 (95.3)
Age at diagnosis	51.4 ± 13.7	54.9 ± 12.2	50.6 ± 12.8	52.1 ± 13.4	55.5 ± 12.4	56.2 ± 12.4	54.4 ± 9.5	54.5 ± 12.1	48.9 ± 13	55.4 ± 9.3
Ethnicity (White)	838/953 (87.9)	164/193 (85)	142/172 (82.6)	95/100 (95)	45/50 (90)	84/94 (89.4)	48/55 (87.3)	44/51 (86.3)	44/46 (95.7)	35/42 (83.3)
Anti-Ro antibodies	739/949 (77.9)	139/192 (72.4)	139/171 (81.3)	81/98 (82.7)	31/49 (63.3)	70/93 (75.3)	37/53 (69.8)	45/52 (86.5)	38/46 (82.6)	29/41 (70.7)
Anti-La antibodies	422/945 (44.7)	91/191 (47.6)	79/168 (47)	65/98 (66.3)	15/49 (30.6)	43/92 (46.7)	27/52 (51.9)	34/52 (65.4)	27/46 (58.7)	21/40 (52.5)
ESSDAI	10.7 ± 12.3	13.9 ± 14.8	10.1 ± 14.2	21.7 ± 19.6	12.4 ± 14.5	17.4 ± 17.8	10.6 ± 12.1	21.5 ± 20	14.2 ± 13	10.9 ± 12.9
ClinESSDAI	11.4 ± 13.4	14.5 ± 15.8	10.4 ± 15.5	23.5 ± 21.4	13.4 ± 15.5	17.5 ± 18.7	11.4 ± 13.4	23.2 ± 21.9	15.3 ± 14	11.9 ± 13.6
ESSDAI domains										
Constitutional	160/956 (16.7)	36/191 (18.8)	29/174 (16.7)	39/100 (39)	8/50 (16)	17/94 (18.1)	16/55 (29.1)	10/52 (19.2)	13/46 (28.3)	7/43 (16.3)
Lymphadenopathy	150/958 (15.7)	20/194 (10.3)	18/174 (10.3)	23/100 (23)	10/50 (20)	9/94 (9.6)	10/55 (18.2)	7/52 (13.5)	11/46 (23.9)	3/43 (7)
Glandular	303/957 (31.7)	80/192 (41.7)	52/174 (29.9)	49/100 (49)	10/50 (20)	31/94 (33)	20/53 (37.7)	19/52 (36.5)	16/46 (34.8)	13/43 (30.2)
Articular	467/957 (48.8)	97/192 (50.5)	70/174 (40.2)	59/100 (59)	25/50 (50)	51/94 (54.3)	25/55 (45.5)	27/52 (51.9)	30/46 (65.2)	21/43 (48.8)
Cutaneous	184/958 (19.2)	33/194 (17)	21/174 (12.1)	25/100 (25)	7/50 (14)	24/94 (25.5)	8/55 (14.5)	13/52 (25)	9/46 (19.6)	7/43 (16.3)
Pulmonary	187/958 (19.5)	52/194 (26.8)	31/174 (17.8)	58/100 (58)	10/50 (20)	36/94 (38.3)	12/55 (21.8)	31/52 (59.6)	11/46 (23.9)	8/43 (18.6)
Renal	82/957 (8.6)	27/192 (14.1)	16/174 (9.2)	31/100 (31)	5/50 (10)	20/94 (21.3)	6/55 (10.9)	14/52 (26.9)	9/46 (19.6)	9/43 (20.9)
Muscular	76/957 (7.9)	24/192 (12.5)	15/174 (8.6)	15/100 (15)	4/50 (8)	13/94 (13.8)	7/55 (12.7)	7/52 (13.5)	4/46 (8.7)	4/43 (9.3)
PNS	126/957 (13.2)	34/192 (17.7)	16/174 (9.2)	14/100 (14)	28/50 (56)	19/94 (20.2)	4/53 (7.5)	11/52 (21.2)	6/46 (13)	5/43 (11.6)
CNS	27/957 (2.8)	8/192 (4.2)	7/174 (4)	7/100 (7)	2/50 (4)	6/94 (6.4)	2/53 (3.8)	2/52 (3.8)	1/46 (2.2)	1/43 (2.3)
Haematological	278/954 (29.1)	55/194 (28.4)	39/173 (22.5)	41/100 (41)	10/50 (20)	26/94 (27.7)	18/55 (32.7)	14/51 (27.5)	16/46 (34.8)	9/43 (20.9)
Biological	552/931 (59.3)	117/180 (65)	111/166 (66.9)	71/97 (73.2)	15/50 (30)	56/81 (69.1)	27/54 (50)	41/51 (80.4)	30/45 (66.7)	21/42 (50)

Our results show that patients with non-ESSDAI systemic features have a specific phenotypic profile: they were diagnosed at a younger age, were more frequently White and have a lower frequency of oral dryness and positive salivary gland biopsy in comparison with those without these features. Another key feature of this subset of patients is their enhanced immunological expression, with an increased frequency of both autoantibodies (anti-Ro and anti-La antibodies) and immunological prognostic markers (cryoglobulins and hypocomplementaemia) that are strongly linked to systemic activity of SS (21). Accordingly, patients with non-ESSDAI systemic activity had a higher frequency of systemic activity in all the organ-specific domains included in the ESSDAI in comparison with patients without these features. This may explain why the mean ESSDAI is nearly twice in patients with non-ESSDAI features (10.3 *vs*. 5.5 in those without). The mean ESSDAI score of the whole population is a little higher than that reported in other European cohorts from UK (4.9), Italy (5) and France (5.3) (22-24). In addition, the presence of non-ESSDAI features was associated with a more severe systemic disease, since the percentage of patients with non-ESSDAI features presenting a high DAS was nearly 3-times higher in comparison with the percentage found in patients without these features (27% *vs*. 11%).

Cardiovascular manifestations were the

most frequent organ-specific group of non-ESSDAI features reported in our patients (17% of the total cohort). RP was reported in 15% of patients, and must be considered largely as the predominant non-ESSDAI systemic feature. The frequency we found is very close to that reported by previous single-centre studies (25, 26), confirming that RP is one of the most frequent systemic features of primary SS. For other cardiovascular features (valvular disease, pericarditis), the frequencies were 1.5% and 0.7%, respectively, suggesting that the clinical relevance of these features in the systemic phenotype of primary SS is very low. However, it should be mentioned that we probably collected those cases with severe clinical presentations, and that some presenting with mild features or even without clinical symptoms maybe were not collected. In fact, the studies using cardiac ultrasound in primary SS patients report a higher frequency of valvular disease of 30–40% (27, 28) and pericardial involvement between 4-33% (27-30), although most patients were asymptomatic (28, 31). The clinical relevance of finding these asymptomatic abnormalities in imaging studies is unclear, with some studies suggesting a significant association with the older age of affected patients (27, 32), although our study, as other previous studies (27, 33), have also reported a close association with immunological markers and systemic activity. Finally, myocarditis in primary SS should be considered as a very rare event (only 2 reported cases), and for Ro-associated congenital heart block, we collected 29 cases among the 4096 Ro+ women included in the study, estimating for the first time a frequency of 7 cases per 1,000 Ro+ primary SS women of this potential life-threatening obstetrical feature (34).

SS-related pulmonary disease is defined in the ESSDAI classification as the presence of either bronchial or interstitial lung disease. We have found additional pulmonary features (pleuritis and PAH) in less than 2.5% of patients, but in spite of the rare frequency, patients presenting with these features had the highest frequencies of both anti-Ro and anti-La antibodies

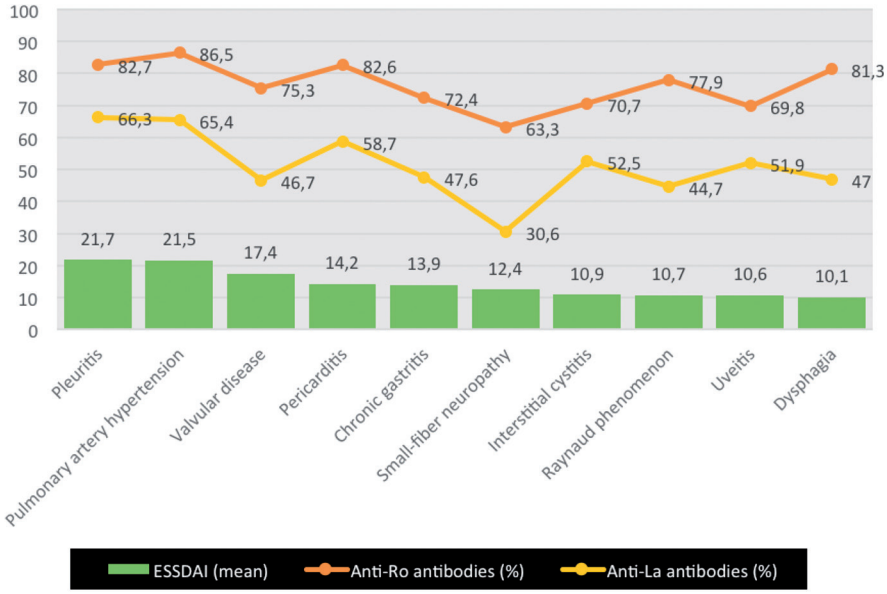

Fig. 1. Mean ESSDAI and frequency of anti-Ro/La antibodies in patients presenting with out of ESSDAI features: analysis of the 10 most frequently reported features.

and also the highest mean ESSDAI values (higher than 20) among all patients with non-ESSDAI features. Previous studies have reported a higher frequency of immunological markers in primary SS patients with PAH, including RF (35-37), cryoglobulins and hypocomplementaemia (27) and anti-Ro antibodies (37). It should be noted the very high frequency of positive anti-La antibodies in these patients (67%) in comparison with the frequency reported in the total cohort (41%), a feature not previously reported. Nearly 60% of patients presenting with pleuritis or PAH had concomitant systemic activity in the pulmonary ESSDAI domain, suggesting a close association with an underlying lung disease, as was reported by Launay *et al*. in 2007 (37).

Out of the cardiopulmonary manifestations, the remaining non-ESSDAI features that we analysed had a very low frequency, confirming the data reported in previous studies for some of these features (38-43). Thereby, the systemic spectrum of primary SS extends out of the ESSDAI either by features corresponding to organs/systems not currently included (digestive, inflammatory ocular, urological, ENT) or by features not included in the corresponding ESSDAI organ-specific domain (cutaneous, peripheral nerve) (Fig. 2). However, the usefulness of including these features when systemic activity of patients with primary SS is measured in the daily practice should be considered very limited taking into account their very low frequency.

In spite of counting on the largest clinical series of patients with primary SS ever analysed, some limitations of the study should be considered. Some results obtained from studies including clinical big data may not be clinically relevant, with further studies being necessary to confirm their relevance in smaller, but more homogeneous, populations. In addition, the retrospective design could promote the predominant inclusion of more severe, clinically-relevant, systemic features instead of milder features, probably underestimating the frequency of most features we have analysed, especially for those that are detected by imaging studies (serosal and valvular involvements, PAH).

Dryness of the mucosal surfaces is still the pivotal clinical involvement that strongly influences the diagnostic approach to primary SS. In the 2016 ACR/EULAR criteria, a suspicion of SS from a positive ESSDAI questionnaire (at least one active domain) is considered an inclusion criteria in the absence of sicca symptoms, but the criteria are even not yet specifically designed to capture the full spectrum of extraglandular features other than the exocrine

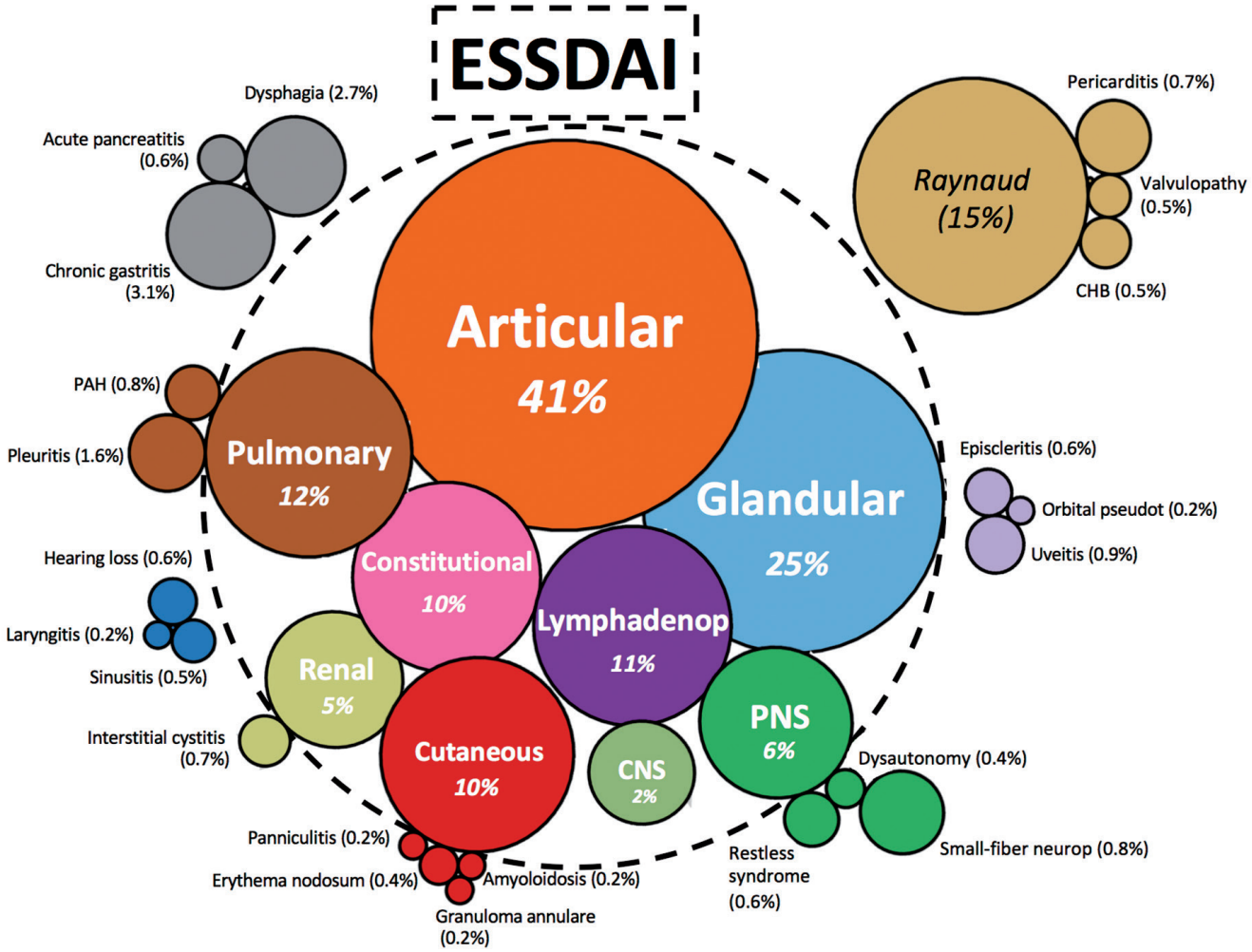

Fig. 2. Frequency of the ESSDAI and non-ESSDAI systemic features.

glands, excluding systemic features (included or not in the ESSDAI) as forming part of the core criteria, which are still focused exclusively on glandular involvement, together with the mandatory presence of only one autoantibody, anti-Ro/SS-A. This highly-restricted diagnostic approach is not seen in the criteria proposed for other similar systemic autoimmune diseases such as systemic lupus erythematosus (SLE) or vasculitis. The results of this study, together with the already-published evidence supporting a pivotal role of systemic disease in primary SS, are pointing out the need of a future re-evaluation about how we are defining, classifying and diagnosing primary SS. Further studies will be needed in order to better stratify the phenotypes of SS with out-of-ESSDAI clinical manifestations and confirm their role in terms of outcome and therapeutic response.

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Competing interests

R. Giacomelli has received speaker honoraria and/or unrestricted research grants from Abbvie, Roche, Actelion, BMS, MSD, Ely Lilly, Pfizer and Sobi.

The other co-authors have declared no competing interests.

APPENDIX

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