## Influence of the age at diagnosis in the disease expression of pSS / S. Retamozo et al.

## Supplementary Table S1. Main studies focused on the characterisation of young-onset primary SS.

First author	Year	Country	Age criteria	Number of	Gender (F)	Sicca symptoms	Oral tests	Ocular tests	Salivary biopsy	Autoantibodies	Systemic disease
Ramos-Casals	1998	Spain	< 35 years	13	13	Xerostomia n= 12 (92%); Xerophthalmia n=12 (92%) (not detailed)	NA	Positive Schirmer's eye test and=or rose Bengal staining n=13 (100%) (not detailed)	Lymphocytic infiltrates grade 3 or 4 in 9 out of 11 (82%) (not detailed)	ANA n= 8 (62%), RF n= 9 (70%), anti-Ro=SS-A n= 9 (70%); anti-La=SS-B n= 4 (31%). Compared with patients with older onset ( $\geq$ 35 years), young onset had a higher prevalence of RF (70% $vs$ . 39%, $p$ =0.034), anti-Ro=SS-A antibodies (70% $vs$ . 28%, $p$ =0.004) and monoclonal immunoglobulins (23% $vs$ . 4%, $p$ =0.02) in their sera.	Articular (31%), peripheral neuropathy (23%), cutaneous vasculitis (23%) and Raynaud's phenomenon (23%). Patients with a younger onset vs. older onset (≥ 35 years), presented a higher prevalence of lymphadenopathy (54% vs. 6%, p<0.001, OR 17.9, CI 4.1±81.8). The prevalence of recurrent parotidomegaly or splenomegaly were also more common in patients with a young onset developed ymphoproliferative disease, lcompared with one patient of the older-onset group (23% vs. 1%, p=0.002, OR 39, IC 3.1±1976.2).
Haga	1999	Norway	< 45 years	16	NA	NA	Unstimulated whole sialometry showed normal values in 31 pts. (Not detailed)	Schirmer I and UWS correlated to s-IgG (p<0.01), anti-SSA/SSB (p<0.02), and RF (p<0.05). The combination of ANA, anti-SSA/SSB and RF correlated to the surface index (p<0.02), but not to any of the other indices for disease manifestations in young patients.	biopsy of the minor salivary glands was high, but NS different in the three age groups.	ANA (87.5%); Anti-SSA/SSB (62.5%); RF (62.5%); presence of ANA, anti- SSA/SSB (50%). The age at diagnosis (<45 years) correlated to the presence of the serological parameters anti- SSA/SSB (p< 0.02) RF (p< 0.01), s-IgG (p <0.05) and so did the presence of the combination of ANA, anti-SSA/ SSB and RF (p<0.02) compared to patients to middle aged (diagnosed 45 - 60 years) and old patients (≥60 years).	
Ramos-Casals	2008	Spain	<35 years	137	NA	Lower xerostomicompared with those aged >35 years	ia NA	Lower positive ocular tests compared with those aged >35 years	NA	Higher prevalence of immunologic markers (RF >25 UI/L = 83/132 (63%), Anti-Ro/ SS-A (+)= 101/135 (75%), Anti-La/ SS-B (+) = 68/135 (50%)) were found in patients aged <35 years compared with those aged >35 years.	
Botsios	2011	Italy	< 40 years	130	127 (98)	Xerostomia  xerophthalmia n= 102 (78.5). NS between three groups: elderly (> 65 years), adult (> 40 and ≤65 years), and youn (≤40 years).	UWSF (≤1.5mL n= 94 (72.3); n= 78 (60); salivary sialography (score≥1 according to Rubin e Holt) n= 88 (67.6). g NS between three groups elderly (> 65 years), adult (>40 and ≤65 years), aduly (≤40 years).	Schirmer I test in 15 minutes) Rose-Bengal (score ≥4) n= 43 (33.3). NS between three groups: elderly (> 65 years), adult (> 40 and ≤65 years), and young (≤40 years).	Focus score n= 86 (66.1); NS between three groups: elderly (> 65 years), adult (> 40 and ≤65 years), and young (≤40 years).	ANA + (titre ≥1 n= 71(64.5). (92.8); Anti-Ro+ n= 109 (83.9); anti-La+ n= 82 (63); RF > 40 IU/L n= 95 (75.8) NS between three groups: elderly (> 65 years), adult (> 40 and ≤65 years), and young (≤40 years).	Arthralgia n= 96 (73.9); > 1:80) n= 117 arthritis n= 48 (36.9); Raynaud's phenomenon n= 34 (26.1), lymphadenopathy n=28 (21.5); purpura n= 29 (22.3). NS between three groups: elderly (> 65 years), adult (> 40 and ≤65 years), and young (≤40 years).

First author	Year	Country	Age criteria	Number of patients	Gender (F)	Sicca symptoms	Oral tests	Ocular tests	Salivary biopsy	Autoantibodies	Systemic disease
Theander	2015	Sweden	< 40 years	•	NA	NA NA	NA	NA	NA	In 23 patients, primary SS was diagnosed before age 40. These patients showed a significantly higher prevalence of pre-diagnostic autoantibodies (ANAs, RF, and autoantibodies against Ro 60/SSA, Ro 52/SSA, and La/SSB) compared with those ages 40–60 years (n=56) or 60 years (n=56) or 60 years (n=38) at diagnosis. The prevalence of autoantibodies after diagnosis was also higher in patients with early-onset disease than in those with late-onset disease RF (p=0.04 and p=0.028 for patients with early-onset disease vs 40 and 60 years and vs older than 60, respectively), and Ro 60/SSA (p=0.00 for both comparisor Ro 52/SSA (p=0.02 and P50.006), and La/SSB (p=0.020 and p=0.007), but not for ANAs.	e 4
Zhao	2015	China	<35 years	75 (5.3%)	NA	Sicca symptoms, n (%) 46/72 (63.9); xerophthalmia, n (%) 10 (37.0) were observed less frequently.	NA	NA	NA	Higher prevalence of high IgG levels and low C3 levels were found at diagnosis in <35 years compared with > 35 years	Purpura, n (%) 24/349 (6.9); flaccid paralysis due to hypokalemia n=17/373 (4.6), flaccid paralysis due to hypocytosis, n (%) 33/373 (8.8). Higher prevalence of purpura and flaccid paralysis resulting from hypokalemia and pancytopenia were found at diagnosis in <35 years compared with > 35 years.
Nakanishi	2016	Japan	<60 years	87	83 (95%)	Xerostomia, n (%) 42 (51%); Xerophthalmia = 34 (41%). Compared to the younger age group (<60 years), the older patients were more likely to have dry mouth.	NA	NA	NA	and or anti-SSB antibodies n= 82 (94%); ANA>	Arthritis n=12 (11%); PN n=6 (6.9%); aseptic meningitis n=4 (4.6%); lymphoma n=2 (2.3%) $vs$ . n=7 (12) elderly $p$ =0.03. The younger patients had a greater likelihood of arthritis and a photosensitive rash ( $p$ <0.05).
Anquetil	2019	France	<35 years	55	NA	Xerostomia 21/55 (38.2) NS; Xerophthalmia 28/44 (63.6) NS compared with age >35 years.	NA	NA	NA	ANA younger was $86.5\%$ vs. $73.1\%$ for the later onset group $(p = 0.038)$ , $84.6\%$ presented anti-SSA vs. $54.4\%$ $(p < 0.001)$ and $57.7\%$ presented anti-SSB vs. $29.7\%$ $(p < 0.001)$ . RF was positive in $41.5\%$ vs. $20.2\%$ $(p < 0.001)$ . Anti-SSA antibodies was statistically associated with early-onset pSS $(OR = 3.23, 95\%)$ CI $1.43, 7.31$ .	>35 years. ESSDAI NS at diagnosis. The variation in ESSDAI scores between baseline and the 5-yea r follow-up was significant

First author	Year	Country	Age criteria	Number o patients	f Gender (F)	Sicca symptoms	Oral tests	Ocular tests	Salivary biopsy	Autoantibodies	Systemic disease
Lee	2021	South Korea	< 40 years	23	21 (91.3)	Xerostomia, n (%)21 (91.3); xerophthalmia, n (%) 17 (73.9) NS between EopSS (≥ 65 years), adult-onse (AopSS) (≥ 40 and < 65 years), and young-onset (YopSS) (< 40 years).		Schirmer's test,	Focus score 1 (1, 2) NS between 3 groups	ANA≥ 1:160, n (%) 18 (78.3); anti- Ro/SSA, n (%) 22 (95.7); anti- La/SSB, n (%) 12 (52.2); RF, IU/dl 31.5 (14.3, 54.5). YopSS had higher positivity of anti- Ro/SSA and anti- La/SSB compared to those with EopSS and AopSS.	significantly higher frequency of arthritis (39.1%, 7% and 22.6%, respectively, $p < 0.01$ ) than those with EopSS and
Alunno	2021	Italy	< 40 years	64	60 (94)	Xerostomia < 40 years n=56 (87% vs. ≥ 40 and < 65 n=142 (84%) vs. Onset ≥ 65 years n= 44 (80%) p= NS. Xerophtalmi < 40 years n=57 (89%) vs. ≥ 40 and < 65 n=145 (86%) vs. Onset ≥ 65 years n= 48 (87%) p= NS	) ;	NA NA	NA	Neither anti-Ro nor anti-La < 40 years n= 10 (16%) vs. ≥ 40 and < 65 n=52 (31%) vs. Onset ≥ 65 years n= 28 (51%) NS; Anti-Ro only < 40 years n= 15 (23%) vs ≥ 40 and < 65 n= 63 (37%) vs. ≥ 65 years n= 17 (31%) NS; Anti-La only < 40 years n= 1 (1.5%) vs. ≥ 40 and < 65 n= 4 (2%) vs. ≥ 65 years n= 1 (2%) NS; both anti-Ro and anti-La < 40 years n= 29 (45%) vs ≥ 40 and < 65 n= 49 (29%) vs. ≥ 6 years n= 18 (33%) NS; RF < 40 years n=35 (55%) vs. ≥ 40 and < 65 n= 74 (44%) vs. ≥ 65 years n= 20 (36%) p < 0.01.	5

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## Supplementary Table S2. Main studies focused on the characterisation of elderly-onset primary SS.

First author	Year	Country	Age criteria	Number of patients	f Gender (F)	Sicca symptoms	Oral tests	Ocular tests	Salivary biopsy	Autoantibodies	Systemic disease
García- Carrasco	1999	Spain	> 70 years	31 (14%)	26	Xerostomia, n (%) =30 (97%); Xerophthalmia n= 28 (90%). NS compared with onset <70 y	NA	NA	3 or 4 (Chisholm ± Mason classification)	n= 5 (17%), anti- La=SSB n= 5 (17%). NS compared with onset <70 y	Articular involvement (29%), hepatic involvement (20%), peripheral neuropathy (16%) and interstitial pneumopathy (13%). NS compared with onset <70 y
Tishler	2001	Israel	≥ 65 years	: 17	16	Xerostomia n=17 (100); Xerophthalmia n=16 (94) NS between <65 vs. > 65 years	NA	NA	NA	ANA n=6 (36); anti-Ro(SSA) n= 2 (12); anti-La(SSB) n= 2 (12); RF n=2 (12) . RF and anti- Ro(SSA) antibodies were more common in the YOD group (p=0.012  and  p= 0.023, respectively)	Raynaud's n= 2 (12); articular involvement n=3 (18). NS differences were noted in the clinical disease manifestations between the 2 groups of patients (<65 vs. > 65 years)
Ramos-Casals	2008	Spain	> 70 years	156	NA	NA	NA	NA	NA	A lower frequency of Anti-Ro/SS-A (+) = 61/156 (39%) was found in patients aged > 70 years compared with those aged < 70 years	Lower frequency of arthralgia, Raynaud's phenomenon and a higher prevalence of pulmonary involvement 26 (17%) were found in patients aged > 70 years compared with those aged < 70 years
Botsios	2011	Italy	≥ 65 years	21 (6%)	20 (95%)	Xerostomia, n (%) 15 (71.4%); Xerophthalmia= 16 (76.1%). NS between three groups: elderly (> 65 years), adult (> 40 and <65 years), and young (≤40 years).	UWSF showed normal values; positivity for salivary sialography n=12 (57.1%). NS between three groups: elderly (> 65 years), adult (> 40 and ≤65 years), and young (≤40 years).	Schirmer's I n= 17 (80%); Rose- Bengal staining n= 9 (44.4%). NS between three groups: elderly (> 65 years), adult (> 40 and ≤65 years), and young (≤40 years).	A focus score greater or equal to 1 per 4mm² was demonstrated in 11 (53.3%) of the 21 cases. NS between three groups: elderly (> 65 years), adult (> 40 and ≤65 years), and young (≤40 years).		Arthralgias n= 14 (66.7%), Raynaud's phenomenon n= 5 (23.8%); purpura n= 3 (14.2%). NS between three groups: elderly (> 65 years), adult (> 40 and $\leq$ 65 years), and young ( $\leq$ 40 years).
Chebbi	2015	Tunisie	≥ 65 years	18	17 (94.5%)	Xerostomia n=18 (100); Xerophthalmia n=18 (100); Keratoconjuncti- vitis sicca n=12 (66.6%). NS between elderly vs. ≤ 65 years	Salivary gland scintigraphy, performed in 16 patients, revealed poor uptake of the salivary glands in 15 cases (93.7%). NS between elderly vs. ≤ 65 years	Abnormal Schirmer's test, n (%) 18 (100). NS between elderly vs. ≤ 65 years	Stage III or IV of the Chisholm classification in 88.8% of cases. NS between elderly vs. ≤ 65 years	ANA elderly n=8 $(44.4\%) \ vs. \le 65$ years N= 34 $(80.9\%) \ p=0.005$ , anti-SSA elderly n=6 $(33.3\%) \ vs. \le 65$ years N= 29 $(69\%) \ p=0.01$ and anti-SSB antibodies elderly n=3 $(16.6\%) \ vs. \le 65$ years N= 19 $(45.2\%) \ p=0.035$ were significantly higher in young subjects	Extra-glandular manifestations n= 17 (94.5%). Joint involvement n= 16 (88.8%) (arthralgias n= 15, arthritis n=1). Neuropsychiatric manifestations n=7 (38.8%). PNS n= 6 (33.3%). CNS n= 5 (27.7%). Lung involvement n= 8 patients (44.4%). Renal impairment of distal tubular acidosis n= 2 (11.1%). Purpura n= 1. Pulmonary in the elderly n=8 (44.4%) $vs. \le 65$ years n=6 (14.2%) $p=0.019$
Nakanishi	2016	Japan	≥ 60 years	60 (41%)	51 (91%)	Xerostomia, n (%) 42 (79%); Xerophthalmia = 24 (45%). Compared to the younger age group (<60 years; the older patients were more likely to have dry mouth		NA	NA	Anti-SSA antibodies and or anti-SSB antibodies n= 53 (88%); ANA > 1/320 n= 23 (44%); RF n=20 (56%). NS compared with < 60 years	ILD n= 4 (6.7%); CBP n=13 (22%); lymphoma n=7 (12) s vs. younger n=2 (2.3%) p=0.03. Compared to the younger age group, the older patients were more likely to have primary biliary cirrhosis, lymphoma and thrombocytopenia.

First author	Year	Country	Age criteria	Number of patients	Gender (F)	Sicca symptoms	Oral tests	Ocular tests	Salivary biopsy	Autoantibodies	Systemic disease
Lacombe	2020	France	≥ 50 years	105	NA	Subjective DES < 50 years old n=40 (95.2%) vs ≥ 50 years old n=95 (90.5%) < 0.01	UWS flow (mL/min) 0.20 . [0.07–0.33]; UWS flow rate ≤ 0.1 mL/min n= 40 (38.1%). UWS had poor diagnostic performances whatever the threshold in the women ≥ 50 group.	Schirmer (mm/5 min) < 50 years n=5 [1–17.3] $vs$ . ≥ 50 years n=1 [0–4] < 0.001. Schirmer ≤ 5 mm/5 min < 50 years n 25 (59.5%) $vs$ . ≥ 50 years n= 90 (85.7%) < 0.001. OSS ≥ 5 (if examination was realized) < 50 years n= 2/10 (20.0%) $vs$ . ≥ 50 years n= 8/29 (27.6%) 0.51	on MSGB < 50 years n= 17 $(40.5\%) vs. \ge 50$ years n= 61 (58.1%) p=0.051	Anti-SSA antibodies < 50 years n= 9 (21.4%) $vs. \ge 50$ years n = 22 (21.0%) $p$ =0.35; Anti-SSB antibodies < 50 years n= 6 (14.3%) $vs$ $\ge 50$ years n=16 (15.2%) $p$ =0.95; ANA > 1/200 < 50 years n=12 (28.6%) $vs. \ge 50$ years n = 32 (30.5%) $p$ =0.96	NA
Lee	2021	South Korea	≥ 65 years	43 (19.5%)	40 (93.0%)		USFR, ml/minute 0.1 (0, 0.25); SGUS score ≥ 14 was significantly lower in the elderly (44.2%) than in the AopSS (64.5%) and YopSS (78.3%) (è < 0.05) groups	Schirmer's test,	Focus score (1, 1.75) NS between 3 groups	EopSS had significantly lower positivity of anti-Ro/SSA and anti-La/SSB compared to those with AopSS and YopSS.	EopSS had significantly higher frequency of ILD (51.2% $vs$ . 13.5% and 8.7%, respectively, $p < 0.001$ ) and lower frequency of arthritis (7% $vs$ . 22.6%, and 39.1%, respectively, $p < 0.01$ ) than those with AopSS and YopSS ESSDAI was significantly higher in EopSS than in opSS (3 $vs$ . 2, $p < 0.01$ ).
Alunno	2021	Italy	≥ 65 years	55	55	Xerostomia < 40 years n=56 (87% vs. ≥ 40 and < 65 n=142 (84%) vs. onset ≥ 65 years n= 44 (80%) p= NS. Xerophthalmia < 40 years n=57 (89%) vs. ≥ 40 and < 65 n=145 (86%) vs. onset ≥ 65 years n= 48 (87%) p= NS	)	NA .	NA .	Neither anti-Ro nor anti-La < 40 years n= 10 (16%) vs. ≥ 40 and < 65 n=52 (31%) vs. onset ≥ 65 years n= 28 (51%) NS; Anti-Ro only < 40 years n= 15 (23%) vs. ≥ 40 and < 65 n=63 (37%) vs. ≥ 65 years n= 17 (31%) NS; Anti-La only < 40 years n= 1 (1.5%) vs. ≥ 40 and < 65 n= 4 (2%) vs. ≥ 65 years n= 1 (2%) NS; both anti-Ro and anti-La < 40 years n= 29 (45%) vs. ≥ 40 and < 65 n= 49 (29%) vs. ≥ 65 years n= 18 (33%) NS; RF < 40 years n=35 (55%) vs. ≥ 40 and < 65 n=74 (44%) vs. ≥ 65 years n= 20 (36%) p < 0.01.	