

# **Influence of the age at diagnosis in the disease expression of primary Sjögren syndrome. Analysis of 12,753 patients from the Sjögren Big Data Consortium.**

Soledad Retamozo<sup>1</sup>, Nihan Acar-Denizli<sup>2</sup>, Ildiko Fanny Horváth<sup>3</sup>, Wan-Fai Ng<sup>4</sup>, Astrid Rasmussen<sup>5</sup>, Xu Dong<sup>6</sup>, Xiaomei Li<sup>7</sup>, Chiara Baldini<sup>8</sup>, Peter Olsson<sup>9</sup>, Roberta Priori<sup>10, 11</sup>, Raphaelae Seror<sup>12</sup>, Jacques-Eric Gottenberg<sup>13</sup>, Aike A. Kruize<sup>14</sup>, Gabriela Hernandez-Molina<sup>15</sup>, Arjan Vissink<sup>16</sup>, Pulukool Sandhya<sup>17</sup>, Berkan Armagan<sup>18</sup>, Luca Quartuccio<sup>19</sup>, Agata Sebastian<sup>20</sup>, Sonja Praprotnik<sup>21</sup>, Elena Bartoloni Bocci<sup>22</sup>, Seung-Ki Kwok<sup>23</sup>, Marika Kvarnstrom<sup>24</sup>, Maureen Rischmueller<sup>25</sup>, Roser Solans<sup>26</sup>, Damien Sene<sup>27</sup>, Sandra G. Pasoto<sup>28</sup>, Yasunori Suzuki<sup>29</sup>, David Isenberg<sup>30</sup>, Valeria Valim<sup>31</sup>, Gunnel Nordmark<sup>32</sup>, Hideki Nakamura<sup>33</sup>, Virginia Fernandes Moça Trevisani<sup>34</sup>, Benedikt Hofauer<sup>35</sup>, Antoni Sisó-Almirall<sup>36</sup>, Roberto Giacomelli<sup>37</sup>, Valerie Devauchelle-Pensec<sup>38</sup>, Michele Bombardieri<sup>39</sup>, Fabiola Atzeni<sup>40</sup>, Daniel Hammenfors<sup>41</sup>, Brenda Maure<sup>42</sup>, Steven E. Carsons<sup>43</sup>, Tamer Gheita<sup>44</sup>, Isabel Sánchez-Berná<sup>45</sup>, Miguel López-Dupla<sup>46</sup>, Jacques Morel<sup>47</sup>, Nevsun Inanç<sup>48</sup>, Eva Fonseca-Aizpuru<sup>49</sup>, César Morcillo<sup>50</sup>, Cristina Vollenveider<sup>51</sup>, Sheila Melchor-Díaz<sup>52</sup>, Marcos Vázquez<sup>53</sup>, Ericka Díaz-Cuiza<sup>54</sup>, Sandra Consani-Fernández<sup>55</sup>, Borja de-Miguel-Campo<sup>56</sup>, Antónia Szántó<sup>3</sup>, Stefano Bombardieri<sup>8</sup>, Angelica Gattamelata<sup>10</sup>, Anneline Hinrichs<sup>14</sup>, Jorge Sánchez-Guerrero<sup>15</sup>, Debashish Danda<sup>17</sup>, Levent Kilic<sup>18</sup>, Salvatore de Vita<sup>19</sup>, Piotr Wiland<sup>20</sup>, Roberto Gerli<sup>22</sup>, Sung-Hwan Park<sup>23</sup>, Marie Wahren-Herlenius<sup>24</sup>, Hendrika Bootsma<sup>57</sup>, Xavier Mariette<sup>12</sup>, Manuel Ramos-Casals<sup>58</sup> and Pilar Brito-Zerón<sup>50</sup>.

<sup>1</sup> Instituto Modelo de Cardiología Privado SRL, Córdoba, Argentina. Instituto Universitario de Ciencias Biomédicas de Córdoba (IUCBC), Córdoba- Argentina.

<sup>2</sup> Department of Statistics, Faculty of Science and Letters, Mimar Sinan Fine Arts University, Istanbul, Turkey.

<sup>3</sup> Division of Clinical Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary.

<sup>4</sup> Institute of Cellular Medicine, Newcastle University, and NIHR Biomedical Research Centre, Newcastle Upon Tyne, UK.

<sup>5</sup> Genes and Human Disease Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA.

<sup>6</sup> Department of Rheumatology, Peking Union Medical College Hospital, Beijing, China.

<sup>7</sup> Department of Rheumatology and Immunology, Anhui Provincial Hospital, Hefei, China.

<sup>8</sup> Rheumatology Unit, University of Pisa, Pisa, Italy.

<sup>9</sup> Department of Rheumatology, Skane University Hospital Malmö, Lund University, Lund, Sweden.

<sup>10</sup> Department of Internal Medicine and Medical Specialties, Rheumatology Clinic, Sapienza University of Rome, Rome, Italy.

<sup>11</sup> Saint Camillus International University of Health Science, UniCamillus, Rome, Italy.

<sup>12</sup> Center for Immunology of Viral Infections and Autoimmune Diseases, Assistance Publique – Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, Université Paris Sud, INSERM, Paris, France.

<sup>13</sup> Department of Rheumatology, Strasbourg University Hospital, Université de Strasbourg, CNRS, Strasbourg, France.

<sup>14</sup> Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands.

<sup>15</sup> Immunology and Rheumatology Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. México City, Mexico.

<sup>16</sup> Department of Oral and Maxillofacial Surger, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

<sup>17</sup> Department of Clinical Immunology & Rheumatology, Christian Medical College & Hospital, Vellore, India.

<sup>18</sup> Department of Internal Medicine, Hacettepe University, Faculty of Medicine, Ankara, Turkey.

<sup>19</sup> Clinic of Rheumatology, Department of Medical and Biological Sciences, University Hospital "Santa Maria della Misericordia", Udine, Italy.

- <sup>20</sup> Department of Rheumatology and Internal Medicine, Wroclaw Medical Hospital, Wroclaw, Poland.
- <sup>21</sup> Department of Rheumatology, University Medical Centre, Ljubljana, Slovenia.
- <sup>22</sup> Rheumatology Unit, Department of Medicine, University of Perugia, Perugia, Italy.
- <sup>23</sup> Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea.
- <sup>24</sup> Department of Medicine, Solna, Division of Experimental Rheumatology, Karolinska Institutet, and Karolinska University Hospital, Stockholm, Sweden.
- <sup>25</sup> Department of Rheumatology, The Queen Elizabeth Hospital, Discipline of Medicine, University of Adelaide, South Australia, Australia.
- <sup>26</sup> Department of Internal Medicine, Hospital Vall d'Hebron, Barcelona, Spain.
- <sup>27</sup> Service de Médecine Interne 2, Hôpital Lariboisière, Université Paris VII, Assistance Publique-Hôpitaux de Paris, 2, Paris, France.
- <sup>28</sup> Rheumatology Division, Hospital das Clinicas HCFMUSP, Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil.
- <sup>29</sup> Division of Rheumatology, Kanazawa University Hospital, Kanazawa, Ishikawa, Japan.
- <sup>30</sup> Centre for Rheumatology, Division of Medicine, University College London, London, UK.
- <sup>31</sup> Department of Medicine, Federal University of Espírito Santo, Vitória, Brazil.
- <sup>32</sup> Rheumatology, Department of Medical Sciences, Uppsala University, Uppsala, Sweden.
- <sup>33</sup> Department of Immunology and Rheumatology, Division of Advanced Preventive Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
- <sup>34</sup> Division of Health Based Evidence, Federal University of São Paulo, Sao Paulo, Brazil.
- <sup>35</sup> Otorhinolaryngology, Head and Neck Surgery, Technical University Munich, Munich, Germany.
- <sup>36</sup> Primary Care Centre Les Corts, Consorci d'Atenció Primària de Salut Barcelona Esquerra (CAPSBE), Barcelona, Spain.
- <sup>37</sup> Clinical Unit of Rheumatology, University of l'Aquila, School of Medicine, L'Aquila, Italy.
- <sup>38</sup> Rheumatology Department, Brest University Hospital, Brest, France.
- <sup>39</sup> Centre for Experimental Medicine and Rheumatology, Queen Mary University of London, London, UK.
- <sup>40</sup> IRCCS Galeazzi Orthopedic Institute, Milan and Rheumatology Unit, University of Messina, Messina, Italy
- <sup>41</sup> Department of Clinical Science, University of Bergen; and Department of Rheumatology, Haukeland University Hospital, Bergen, Norway.
- <sup>42</sup> Department of Internal Medicine, Complejo Hospitalario Universitario de Vigo, Spain.
- <sup>43</sup> Division of Rheumatology, Allergy and Immunology, New York University Winthrop Hospital and NYU Langone Health, New York, NY, USA.
- <sup>44</sup> Rheumatology Department, Kasr Al Ainy School of Medicine, Cairo University, Cairo, Egypt.
- <sup>45</sup> Department of Internal Medicine, Hospital Rey Juan Carlos de Móstoles, Madrid, Spain.
- <sup>46</sup> Department of Internal Medicine, Hospital Joan XXIII, Tarragona, Spain.
- <sup>47</sup> Department of Rheumatology, Teaching hospital and University of Montpellier, Montpellier, France.
- <sup>48</sup> Marmara University, School of Medicine, Istanbul.
- <sup>49</sup> Department of Internal Medicine, Hospital de Cabueñes, Gijón, Spain.
- <sup>50</sup> Autoimmune Diseases Unit, Department of Medicine, Hospital CIMA- Sanitas, Barcelona, Spain.
- <sup>51</sup> German Hospital, Buenos Aires, Argentina.
- <sup>52</sup> Department of Rheumatology, Hospital 12 de Octubre, Madrid, Spain.
- <sup>53</sup> Department of Rheumatology, Hospital de Clínicas, San Lorenzo, Paraguay.
- <sup>54</sup> Departamento de Reumatología del Seguro Social Universitario y Consultorio Privado de Reumatología, Sucre, Bolivia.
- <sup>55</sup> Internal Medicine, Hospital Maciel, and Universidad de la República (UdelaR), Montevideo, Uruguay.
- <sup>56</sup> Department of Internal Medicine, Hospital 12 de Octubre, Madrid, Spain.
- <sup>57</sup> Department of Rheumatology & Clinical Immunology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.
- <sup>58</sup> Department of Autoimmune Diseases, ICMiD, University of Barcelona, Hospital Clínic, Barcelona, Spain.

Address reprint requests to: Dr Manuel Ramos-Casals, Servei de Malalties Autoimmunes Sistèmiques, Hospital Clínic, C/Villarroel, 170, 08036-Barcelona, Spain. Phone: 34-93-2275774. FAX: 34-93-2271707. E-mail: mramos@clinic.cat

## ABSTRACT

**Objective.** To analyse how the main components of the disease phenotype (sicca symptoms, diagnostic tests, immunological markers and systemic disease) can be driven by the age at diagnosis of primary Sjögren syndrome (SjS).

**Methods.** By January 2021, the participant centres had included 12,753 patients from 25 countries that fulfilled the 2002/2016 classification criteria for primary SjS. The age at diagnosis was defined as the time when the attending physician confirmed fulfilment of the criteria. Patients were clustered according to age at diagnosis. Fifty clusters with more than 100 observations (from 27 to 76 years) were used to study the influence of the age at diagnosis in the disease expression.

**Results.** There was a consistent increase in the frequency of oral dryness according to the age at diagnosis, with a frequency of < 90% in patients diagnosed at the youngest ages and > 95% in those diagnosed at the oldest ages. The smooth curves that best fitted a linear model were the frequency of dry mouth (adjusted  $R^2$  0.87) and the frequency of abnormal oral tests (adjusted  $R^2$  0.72). Therefore, for each 1-year increase in the age at diagnosis, the frequency of dry mouth increased by 0.13%, and the frequency of abnormal oral diagnostic tests by 0.11%. There was a consistent year-by-year decrease in the frequency of all autoantibodies and immunological markers except for cryoglobulins. According to the linear models, for each 1-year increase in the age at diagnosis, the frequency of a positive result decreased by 0.57% (for anti-Ro antibodies), 0.47% (for RF) and 0.42% (for anti-La antibodies). The ESSDAI domains which showed a more consistent decrease were glandular and lymph node involvement (for each 1-year increase in the age at diagnosis, the frequency of activity decreased by 0.18%), and constitutional, cutaneous, and haematological involvements (the frequency decreased by 0.09% for each 1-year increase). In contrast, other domains showed an ascending pattern, especially pulmonary involvement (for each 1-year increase in the age at diagnosis, the frequency of activity increased by 0.22%), and peripheral nerve involvement (the frequency increased by 0.09% for each 1-year increase).

**Conclusion.** The influence of the age at diagnosis on the key phenotypic features of primary SjS is strong, and should be considered critical not only for designing a personalized diagnostic approach, but also to be carefully considered when analysing

the results of diagnostic tests and immunological parameters, and when internal organ involvement is suspected at diagnosis.

## INTRODUCTION

Primary Sjögren syndrome (SjS) is a systemic autoimmune disease that mainly affects middle-aged women, and has a frequency ranging between 0.01 and 0.72% [1].

Etiopathogenically, SjS targets the exocrine glands, which are infiltrated by lymphocytes [2]. More than 95% of patients present with oral and/or ocular dryness, but may also develop a large number of extraglandular (systemic) manifestations, which may be the presenting manifestation [3]. The key immunological markers are anti-Ro antibodies (the most specific) and cryoglobulins and hypocomplementemia (the main prognostic markers) [4].

Understanding how these factors influence the systemic phenotype could aid the identification at diagnosis of patients who may be more prone to a more-complicated disease and, therefore, determine which patients should be followed more closely and/or treated more intensively [5]. A significant challenge in diagnosing primary SjS is recognizing that it may occur at any age. Although it is diagnosed predominantly in people aged 30-60 years, the epidemiology of primary SjS is a continuum and it has been reported in people aged 2 [6] to 97 years [7]. Studies in small series of patients have suggested a role for the age at diagnosis in the disease phenotype [4]. In these studies, the statistical approach was based on the comparison of the main SjS features between a specific epidemiological onset (defined according to the age at diagnosis) and the remaining patients: a young disease onset was defined according to an age at diagnosis of < 35–40 years, and an elderly onset by an age at diagnosis > 65–70 years. Considering that the definition of “young” or “elderly” disease onset is arbitrary and the statistical limitations of using a dichotomic analysis of a continuous variable such as age, a better methodological approach could be to analyse how the frequency of the main SjS features may change year by year, according to the age at diagnosis. This type of analysis is only possible when big data sources are used, including a sufficiently representative number of patients per year of age at diagnosis, as occurs with the Sjögren Big Data Consortium [8].

The objective of this study was to analyse how the main components of the disease phenotype (sicca symptoms, diagnostic tests, immunological markers and systemic disease) can be driven by the age at diagnosis in the largest reported international, multi-ethnic cohort of patients with primary SjS.

## **MATERIAL AND 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 SjS using worldwide data-sharing cooperative merging of pre-existing clinical SjS databases from leading centres in clinical research in SjS from five continents (see reference 14 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. The codebook containing instructions on the variables and data codification was discussed and approved by the Steering Committee members and was then shared with the consortium partners. Databases from each centre were harmonised into a single database by applying data-cleaning pre-processing techniques. Descriptive statistics and data visualisation methods were used to detect outliers, data errors, missing data and influential observations [9]. Double-checking to correct errors and complete missing information was carried out to minimize incomplete and erroneous data. Inclusion criteria were fulfilment of the 2002 or 2016 classification criteria [10,11]. Exclusion criteria for considering SjS as a primary disease were chronic HCV/HIV infection, previous lymphoproliferative processes, and associated systemic autoimmune diseases. Diagnostic tests for SjS (ocular tests, oral tests and salivary gland biopsy) were carried out according to the recommendations of the European Community Study Group [12]. The study was approved by the Ethics Committee of the Coordinating Centre (Hospital Clinic, Barcelona, Spain, registry HCB/2015/0869).

### **Definition of variables**

The age at diagnosis was defined based on the moment that the attending physician confirmed fulfilment of the 2002 or 2016 criteria. The main disease features at this time were retrospectively collected and analysed. The following clinical variables were selected for harmonization and further refinement: age, sex, ethnicity, country of residence, fulfilment of 2002/2016 criteria items, antinuclear antibodies, rheumatoid factor, C3 and C4 levels, cryoglobulins, and organ-by-organ ESSDAI scores. By January 2021, the participant centres had included 12,753 valid patients from 25 countries. The

epidemiological variables included were age at diagnosis (continuous variable), sex and ethnicity according to FDA definitions [5]. Systemic involvement at diagnosis was classified and scored according to the ESSDAI [13].

### **Statistical analysis**

Descriptive data are presented as mean and standard deviation (SD) for continuous variables and numbers and percentages (%) for categorical variables. Patients were clustered according to age at diagnosis. Fifty clusters with more than 100 observations (from 27 to 76 years) were used to study the influence of the age at diagnosis in the disease expression. For each cluster, the frequency and percentage of positive diagnostic tests for SS, immunological markers and systemic activity were computed. To represent the main increasing and decreasing patterns, smoothed conditional means were calculated. Generalized additive models were used as the smoothing method. Linear regression models were fitted to smooth curves to identify linear increasing and decreasing trends. Slope (beta) and adjusted R-squared coefficients were computed to interpret models fitting. If the regression beta coefficients for each variable were positive (or negative, respectively) and therefore for every 1-unit increase in the age at diagnosis, the outcome variables will increase (or decrease, respectively) by the corresponding beta coefficient value. Adjusted R-squared values higher than 0.8 were considered as well-fitting. All analyses were conducted using the R V.3.6.0 for Windows statistical software package (<https://www.R-project.org/>).

## RESULTS

The baseline characteristics of the cohort are summarized in **Table 1** and included 11,918 (93.5%) women with a mean age at diagnosis of primary SjS of 52.2 (SD 14.6) years. The frequencies of fulfilment of the 2002 classification criteria items (were 91.9% for dry eye (item I), 93.2% for dry mouth (item II), 83.7% for abnormal ocular tests (item III), 82.2% for positive minor salivary gland biopsy (item IV), 79% for abnormal oral diagnostic tests (item V) and 76.9% for positive anti-Ro/La antibodies (item VI). The frequency of other immunological markers at diagnosis was: positive ANA in 80.8% of patients, positive RF in 48.4, low C3 levels in 12.8%, low C4 levels in 13.3% and positive serum cryoglobulins in 7.6% of patients.

### a) Glandular involvement

There was a consistent increase in the frequency of oral dryness according to the age at diagnosis, with a frequency of < 90% in patients diagnosed at the youngest ages and > 95% in those diagnosed at the oldest ages; a similar pattern was found for ocular dryness until an age at diagnosis of 60 years, although in people diagnosed after 60 years, the ascending curve of the frequency of ocular dryness was inverted, showing a sustained decrease. The curves of the age-by-age frequencies corresponding to the results of diagnostic tests showed a similar pattern: a progressive increase in the frequency of abnormal oral results as the age at diagnosis increased, and the same increase for abnormal ocular tests until an age at diagnosis of 60 years and a progressive decline thereafter (**Figure 1**). The regression beta coefficients for each variable were positive and, therefore, for every 1-unit increase in the age at diagnosis, the outcome variables increased by the corresponding beta coefficient value. The smooth curves that best fitted a linear model were the frequency of dry mouth (adjusted  $R^2$  0.87) and the frequency of abnormal oral tests (adjusted  $R^2$  0.72). Therefore, for each 1-year increase in the age at diagnosis, the frequency of dry mouth increased by 0.13%, and the frequency of abnormal oral diagnostic tests by 0.11% (**Table 2**).

### b) Autoantibodies and immunological markers



There was a consistent year-by-year decrease in the frequency of all autoantibodies and immunological markers except for cryoglobulins (**Figure 2**). For the four main autoantibodies, the smooth curves of the age-by-age frequencies for positive results showed a progressive decrease as the age at diagnosis increased. The smooth curves that best fitted a linear model were the frequency of anti-Ro antibodies (adjusted  $R^2$  0.97), ANA (adjusted  $R^2$  0.93), anti-La antibodies (adjusted  $R^2$  0.88), RF (adjusted  $R^2$  0.86) and low C3 levels (adjusted  $R^2$  0.85). The regression beta coefficients for these variables were negative, and according to the linear models, for each 1-year increase in the age at diagnosis, the frequency of a positive result decreased by 0.57% (for anti-Ro antibodies), 0.47% (for RF), 0.42% (for anti-La antibodies), 0.36% (for ANA, although the smooth curve broke the progressive decrease after the age of 70 and started to ascend slowly). The regression beta coefficients for complement levels were also negative, especially for low C3 levels (for each 1-year increase in the age at diagnosis, the frequency of low C3 levels decreased by 0.26%). (**Table 2**).

### **c) Systemic disease measured according to the ESSDAI**

There was a dual pattern of changes in the frequency of activity in the organ-specific ESSDAI domains according to the age at diagnosis, with some manifestations showing a clearly downward trend when people were diagnosed at an older age, and others with an opposite trend (**Figure 3**). The domains which showed a more consistent decrease were glandular and lymph node involvement (for each 1-year increase in the age at diagnosis, the frequency of activity decreased by 0.18%), and constitutional, cutaneous, and haematological involvements (the frequency decreased by 0.09% for each 1-year increase). In contrast, other domains showed an ascending pattern, especially pulmonary involvement (for each 1-year increase in the age at diagnosis, the frequency of activity increased by 0.22%), and peripheral nerve involvement (the frequency increased by 0.09% for each 1-year increase). The smooth curves that best fitted a linear model (adjusted  $R^2 > 0.8$ ) were the frequency of the pulmonary, lymphadenopathy, cutaneous, peripheral nerve, renal, glandular, and constitutional domains (**Table 2**).

## DISCUSSION

Wide individual variations in the phenotypic expression of systemic autoimmune diseases are a serious handicap in studies designed to identify homogeneous disease patterns that may aid early identification of disease. This is especially complicated in studies including few patients, as there is often a lack of significant between-group differences. Thus, studies that have analysed potential correlations between the age at diagnosis and the disease phenotype have used a dichotomous statistical approach in which a specific arbitrary age limit is set, dividing the population into two subsets which are compared. Despite this simplified statistical approach, most studies have included samples of a few dozen patients as the study group (**Supplementary Tables 1 and 2**), making it difficult to identify significant age-dependent between-group differences.

This is the first study to analyse the influence of the age at diagnosis on the key phenotypic features of primary SjS using a statistical approach based on analysis of the year-by-year frequency of each feature according to the age at diagnosis. This is possible due to the size of the Sjögren Big Data Consortium, as the database contains at least 100 patients per year of age at diagnosis. In contrast, the young- or elderly-onset subsets analysed in previous studies included 10-50 participants (**Supplementary Tables 1 and 2**). We used an innovative statistical approach that permitted confirmation of some age-dependent associations previously described in small studies, and the discovery of new associations that would be impossible to detect using dichotomous comparisons between small samples of patients.

The first result to highlight is the clear correlation between the age at diagnosis and the frequency of self-reported oral and ocular dryness. All previous studies but one [14] found no significant differences in the frequency of oral and ocular dryness, using various dichotomous thresholds (<35, 40 or 50 years to define young-onset SjS, or > 60 or 65 years to define elderly-onset SjS). In contrast, we found that the reported frequency of dryness is higher as the age at diagnosis increases, although this pattern differed in patients diagnosed after 60 years of age. Likewise, the frequency of dry mouth increased with age, but the frequency of dry eye decreased after 60 years of age. The key factor influencing salivary flow rate was age [15]: studies in non-autoimmune populations have shown that the frequency of oral dryness is much

higher in older people [16-20]. This has been linked to progressive glandular ageing, and especially with the greater use of drugs in older people which has been closely associated with reduced salivary flow rates [19], especially in patients receiving  $\geq 2$  hyposalivatory drugs [21] and those with coexisting diabetes mellitus [22]. In patients with primary SjS, we confirmed that the frequency of abnormal diagnostic tests according to the age at diagnosis followed the same pattern as that of the corresponding symptoms, that is, a progressive age-dependent increase in the frequency of abnormal oral tests, and the same pattern of an increase and subsequent decrease of the frequency of abnormal ocular tests in people aged  $> 60$  years. Although most studies have reported no significant differences between age of onset subsets in primary SjS [23-25], the study with the most patients [26] reported a higher frequency of abnormal Schirmer tests in women  $> 50$  years. The age-dependent pattern observed for salivary gland biopsy results is less clear, although there was a tendency to a positive result the younger the age at diagnosis. Our results clearly show that the immunological profile is mostly driven by the age at diagnosis, with a marked, sustained decrease in the percentage of positive results for the four main SjS-related autoantibodies the higher the age at diagnosis. The higher immunological positivity in people diagnosed at younger ages has been reported in some [24,25,27-29] but not all [14,23,26] studies. We were able to evaluate the evolution of the frequency of positivity of each marker year-by-year of the age at diagnosis and to detect hitherto undescribed trends, with a differential age-dependent pattern of positive results for ANA vs Ro, La and RF. The pattern for ANA, in which the frequency of positive results gradually decreases until the age of 65 years, after which the trend reverses and increases progressively with age, suggests this could be related to the higher frequency of ANA positivity in older people [30,31]. The age-dependent frequencies of positive results for Ro, La and RF are very similar, and are practically parallel in the case of La and RF, two closely-related immunological parameters in primary SjS patients [32-35]. Immunologically, patients diagnosed at younger ages form a distinct disease subset [36]. In 1998, we reported that young-onset patients had less salivary gland involvement (dry mouth and parotid enlargement) and a higher frequency of immunologic markers (anti-Ro and low C4 levels) [37,38], likewise Haga et al. also reported higher positivity of Ro/La autoantibodies, RF and

hypergammaglobulinemia [39]. This was confirmed by Theander et al. [36] who reported that patients diagnosed before 40 years had the highest frequencies of positive autoantibodies (ANA, RF, Ro 60/SSA, Ro 52/SSA and La/SSB) together with higher titres and more autoantibody specificities in the same samples. Due to the close association between systemic disease and the seropositive phenotype (RF/Ro/La carriers) [40], it seems that some SjS patients are likely to be diagnosed earlier due to the development of systemic disease before glandular dysfunction becomes clinically apparent. Thus, we have recently confirmed that patients carrying RF, anti-Ro and anti-La are diagnosed at a younger mean age [41], and that anti-Ro/SS-A and anti-La/SS-B antibodies are closely associated with global systemic activity, especially anti-Ro/SS-A, whose positivity at diagnosis also correlated with a higher activity score in the articular, cutaneous and renal domains in a Spanish multicentre study [42]. A recent study by Quartuccio et al compared Ro/La+ and Ro/La- patients [43] and found a younger age at diagnosis and a higher frequency of glandular swelling, purpura, leukopenia, lymphoma, low C3, low C4, hypergammaglobulinemia, RF and serum cryoglobulins in Ro/La+ patients. Few studies have analysed the influence of age at diagnosis on the frequency of the main immunological prognostic markers of SjS. Our results showed that low C3 levels are the prognostic parameter most influenced by age at diagnosis, with a frequency of alterations that decreases progressively as the age at diagnosis increases; low C4 levels follow a similar pattern although not as clear, while cryoglobulinemia follows a more oscillating pattern, with a tendency to increase with age.

Analysis of the frequency of people with activity in each of the 12 ESSDAI domains according to the age at diagnosis clearly divides the domains into three differentiated patterns. The first consists of the domains whose frequency is highest among patients diagnosed at a younger age and which decreases with age (glandular, lymphadenopathy, cutaneous, renal and biological domains). The second pattern shows non-linear, undulating frequency curves (articular, general and haematological domains), while the third pattern consists of the domains whose frequency is minimal in patients diagnosed at a younger age and which increases gradually with age (pulmonary, nervous and muscular system domains). Recent **small** studies have reported similar results for some organ involvements, linking a younger age at

diagnosis with lymphadenopathy and salivary gland enlargement that have also been identified as risk factors for lymphoma development [44] [47], while an older age was related with pulmonary involvement [45,46]. Although interstitial lung disease (ILD) is often considered a late manifestation of SjS (17), a high variability of the time of onset of SjS-ILD has been recently reported (12). In some patients with ILD, an underlying SjS may be underdiagnosed, especially challenging in seronegative patients with no or mild sicca symptoms, and a SjS-specific assessment, including minor salivary glands, is highly recommended (Sambatoro). Different pathogenetic mechanisms linked to the age at which the disease is diagnosed may be associated with a differentiated organ-specific systemic damage. However, the reasons why the SjS phenotype varies so widely according to the age at diagnosis is unclear, and factors such as the progressive ageing of the immune system, individual genetic backgrounds or environmental agents may explain the heterogeneous, age-dependent disease phenotype.

In summary, we found that the wide phenotypic variations in the presentation of primary SjS are strongly linked with the age at diagnosis. The frequency of glandular involvement, immunological markers and the type of organ affected are modulated by age. The best examples are the progressive increase of the frequency of dry mouth with age (1.3% increase per each 10 years) and pulmonary involvement (2.2% increase per each 10 years), and the progressive decrease in the frequency of the main autoantibodies (5.7% decrease for anti-Ro, 4.7% for RF and 4.2% for anti-La, respectively) and some ESSDAI domains (4.4% for the biological domain, 1.8% for the lymphadenopathy and glandular domains, respectively). The age at diagnosis of primary SjS should be considered critical for the design of a personalized diagnostic approach, and should also be considered when analysing the results of diagnostic tests and immunological parameters or when ruling out potential internal organ involvement at diagnosis.

**CONFLICT OF INTEREST**

None declared.

**ACKNOWLEDGMENTS**

The authors thank David Buss for editorial assistance

## REFERENCES

1. Brito-Zerón P, Baldini C, Bootsma H, et al. Sjögren syndrome. *Nat Rev Dis Prim* 2016;2:16047.
2. Mariette X, Criswell LA. Primary Sjogren's Syndrome. *N Engl J Med* 2018;378:931–9.
3. Ramos-Casals M, Brito-Zerón P, Sisó-Almirall A, et al. Primary Sjogren syndrome. *BMJ* 2012;344:e3821.
4. Brito-Zerón P, Retamozo S, Ramos-Casals M. Phenotyping Sjogren's syndrome: towards a personalised management of the disease. *Clin Exp Rheumatol* 2018;36 Suppl 1:198–209.
5. Brito-Zerón P, Acar-Denizli N, Zeher M, et al. Influence of geolocation and ethnicity on the phenotypic expression of primary Sjogren's syndrome at diagnosis in 8310 patients: a cross-sectional study from the Big Data Sjogren Project Consortium. *Ann Rheum Dis* 2017;76:1042–50.
6. De Oliveira MA, De Rezende NPM, Maia CMF, et al. Primary Sjogren syndrome in a 2-year-old patient: role of the dentist in diagnosis and dental management with a 6-year follow-up. *Int J Paediatr Dent* 2011;21:471–5.
7. Brito-Zerón P, Acar-Denizli N, Ng W-F, et al. Epidemiological profile and north-south gradient driving baseline systemic involvement of primary Sjogren's syndrome. *Rheumatology (Oxford)*. 2020; 59:2350-2359.
8. Acar-Denizli N, Kostov B, Ramos-Casals M, et al. The Big Data Sjögren consortium: A project for a new data science era. *Clin Exp Rheumatol* 2019; 37 Suppl 118:19-23
9. Giber K, Sánchez-Marré M, Joaquin I. A survey on pre-processing techniques: relevant issues in the context of environmental data mining. *AI Commun Eur J Artif Intell* 2016;29:627–63.
10. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;61:554–8.
11. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome. *Ann Rheum Dis* 2017;76:9–16.
12. Vitali C, Bombardieri S, Moutsopoulos HM, et al. Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. *Arthritis Rheum* 1993;36:340–7.
13. Seror R, Ravaud P, Bowman SJ, et al. EULAR Sjogren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjogren's syndrome. *Ann Rheum Dis* 2010;69:1103–9.
14. Nakanishi K, Kinjo M. AB0463 Clinical Characteristics of Elderly Patients with Primary Sjögren's Syndrome *Annals of the Rheumatic Diseases* 2016;75:1064.
15. Retamozo S, Baldini C, Bootsma H, et al. Therapeutic Recommendations for the Management of Older Adult Patients with Sjogren's Syndrome. *Drugs Aging*. 2021; 38:265-284.
16. Smith CH, Boland B, Daureeawoo Y, et al. Effect of aging on stimulated salivary flow in adults. *J Am Geriatr Soc*. 2013;61:805–8.
17. Affoo RH, Foley N, Garrick R, et al. Meta-analysis of salivary flow rates in young and older adults. *J Am Geriatr Soc*. 2015;63:2142–51.
18. Kagami H, Hayashi T, Shigetomi T, et al. Assessment of the effects of aging and medication on salivary gland function in patients with xerostomia using <sup>99m</sup>Tc-

scintigraphy. *Clin Trial Nagoya J Med Sci.* 1995;58:149–55.

19. Iwasaki M, Borgnakke WS, Yoshihara A, et al. Hyposalivation and 10-year all-cause mortality in an elderly Japanese population. *Gerodontology.* 2018;35:87–94.

20. Handelman SL, Baric JM, Saunders RH, et al. Hyposalivatory drug use, whole stimulated salivary flow, and mouth dryness in older, long-term care residents. *Spec Care Dentist.* 1989;9:12–8.

21. Chávez EM, Borrell LN, Taylor GW, et al. A longitudinal analysis of salivary flow in control subjects and older adults with type 2 diabetes. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2001;91:166–73.

22. Närhi TO, Vehkalahti MM, Siukosaari P, et al. Salivary findings, daily medication and root caries in the old elderly. *Caries Res.* 1998;32:5–9.

23. Botsios C, Furlan A, Ostuni P, et al. Elderly onset of primary Sjögren's syndrome: clinical manifestations, serological features and oral/ocular diagnostic tests. Comparison with adult and young onset of the disease in a cohort of 336 Italian patients. *Joint Bone Spine.* 2011; 78:171-4.

24. Chebbi W, Ben Salem W, Klii R, et al. Primitive Sjögren syndrome in the elderly: clinical and immunological characteristics. *Pan Afr Med J.* 2015; 20:8.

25. Lee KA, Choi W, Kim J, et al. Elderly-onset primary Sjogren's syndrome focused on clinical and salivary gland ultrasonographic features. *Joint Bone Spine.* 2021; 88:105132.

26. Lacombe V, Lacout C, Lozac'h P, et al. Unstimulated whole saliva flow for diagnosis of primary Sjögren's syndrome: time to revisit the threshold? *Arthritis Res Ther.* 2020; 22:38.

27. García-Carrasco M, Cervera R, Rosas J, et al. Primary Sjögren's syndrome in the elderly: clinical and immunological characteristics. *Lupus.* 1999; 8:20-3.

28. Tishler M, Yaron I, Shirazi I, et al. Clinical and immunological characteristics of elderly onset Sjögren's syndrome: a comparison with younger onset disease. *J Rheumatol.* 2001; 28:795-7.

29. Alunno A, Carubbi F, Ferri C, et al. Different clinical presentations of primary Sjögren's syndrome: Not only a matter of age. Comment on: "Elderly-onset primary Sjögren's syndrome focused on clinical and salivary gland ultrasonographic features by Lee et al. *Joint Bone Spine.* 2021; 88:105132". *Joint Bone Spine.* 2021; 88:105191.

30. Ramos-Casals M, Brito-Zerón P, López-Soto A, et al. Systemic autoimmune diseases in elderly patients: atypical presentation and association with neoplasia. *Autoimmun Rev.* 2004; 3:376-82.

31. Ramos-Casals M, García-Carrasco M, Brito MP, et al. Autoimmunity and geriatrics: clinical significance of autoimmune manifestations in the elderly. *Lupus.* 2003; 12:341-55.

32. Cafaro G, Perricone C, Baldini C, et al. Significance of anti-La/SSB antibodies in primary Sjögren's syndrome patients with combined positivity for anti-Ro/SSA and salivary gland biopsy. *Clin Exp Rheumatol.* 2020;38 Suppl 126:53-56.

33. Ben-Eli H, Solomon A, Aframian DJ, et al. Serological and hematological characteristics of Sjogren's syndrome and dry eye syndrome patients using a novel immune serology technique. *PLoS One.* 2020; 15:e0244712.

34. Atkinson JC, Travis WD, Slocum L, et al. Serum anti-SS-B/La and IgA rheumatoid factor are markers of salivary gland disease activity in primary Sjögren's syndrome. *Arthritis Rheum.* 1992; 35:1368-72.

35. Horsfall AC, Venables PJ, Allard SA, et al. Co-existent anti-La antibodies and



rheumatoid factors bear distinct idiotypic markers. *Scand J Rheumatol Suppl.* 1988;75:84-8.

36. Theander E, Jonsson R, Sjöström B, et al. Prediction of Sjögren's Syndrome Years Before Diagnosis and Identification of Patients With Early Onset and Severe Disease Course by Autoantibody Profiling. *Arthritis Rheumatol (Hoboken, NJ)* 2015;67:2427-36.

37. Ramos-Casals M, Solans R, Rosas J, et al. Primary Sjögren syndrome in Spain: clinical and immunologic expression in 1010 patients. *Medicine (Baltimore)* 2008;87:210-9.

38. Ramos-Casals M, Cervera R, Font J, et al. Young onset of primary Sjögren's syndrome: clinical and immunological characteristics. *Lupus* 1998; 7:202-6.

39. Haga HJ, Jonsson R. The influence of age on disease manifestations and serological characteristics in primary Sjögren's syndrome. *Scand J Rheumatol* 1999; 28:227-32.

41. Brito-Zerón P, Acar-Denizli N, Ng WF, et al. How immunological profile drives clinical phenotype of primary Sjögren's syndrome at diagnosis: analysis of 10,500 patients (Sjögren Big Data Project). *Clin Exp Rheumatol.* 2018; 36 Suppl 112:102-112.

42. Ramos-Casals M, Brito-Zerón P, Solans R, et al. Systemic involvement in primary Sjögren's syndrome evaluated by the EULAR-SS disease activity index: Analysis of 921 spanish patients (GEAS-SS registry). *Rheumatol (United Kingdom)* 2014; 53:321-31.

43. Quartuccio L, Baldini C, Bartoloni E, et al. Anti-SSA/SSB-negative Sjögren's syndrome shows a lower prevalence of lymphoproliferative manifestations, and a lower risk of lymphoma evolution. *Autoimmun Rev* 2015;14:1019-22.

44. Baldini C, Ferro F, Luciano N, et al. Artificial neural networks help to identify disease subsets and to predict lymphoma in primary Sjögren's syndrome. *Clin Exp Rheumatol* 2018;36 Suppl 1:137-44.

45. Ramirez Sepulveda JI, Kvarnstrom M, Eriksson P, et al. Long-term follow-up in primary Sjögren's syndrome reveals differences in clinical presentation between female and male patients. *Biol Sex Differ* 2017; 8:25.

46. Kakugawa T, Sakamoto N, Ishimoto H, et al. Lymphocytic focus score is positively related to airway and interstitial lung diseases in primary Sjögren's syndrome. *Respir Med* 2018; 137:95-102.

47. Goules AV, Argyropoulou OD, Pezoulas VC, et al. Primary Sjögren's Syndrome of Early and Late Onset: Distinct Clinical Phenotypes and Lymphoma Development. *Front Immunol.* 2020; 11:594096.

**48. Ramos-Casals M, Brito-Zerón P, Bombardieri S, et al; EULAR-Sjögren Syndrome Task Force Group. EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. *Ann Rheum Dis.* 2020; 79:3-18.**

**Luppi F, Sebastiani M, Silva M, et al. Interstitial lung disease in Sjögren's syndrome: a clinical review. *Clin Exp Rheumatol.* 2020;38 Suppl 126:291-300**

**Sambataro G, Ferro F, Orlandi M, et al. Clinical, morphological features and prognostic factors associated with interstitial lung disease in primary Sjögren's syndrome: A systematic review from the Italian Society of Rheumatology. *Autoimmun Rev.* 2020; 19:102447.**

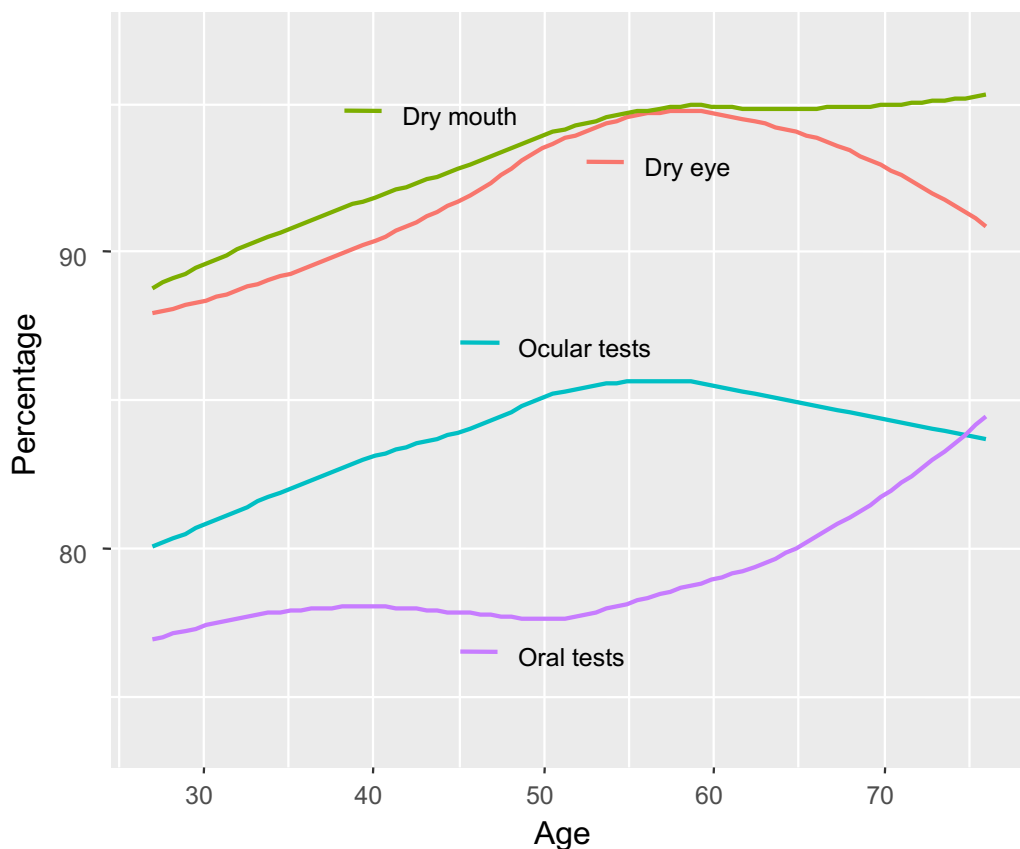
## FIGURE LEGENDS

**Figure 1.** Smooth curves (with 95% confidence intervals) representing the association between age at diagnosis and the frequency at presentation of the main symptoms and diagnostic tests related to glandular involvement

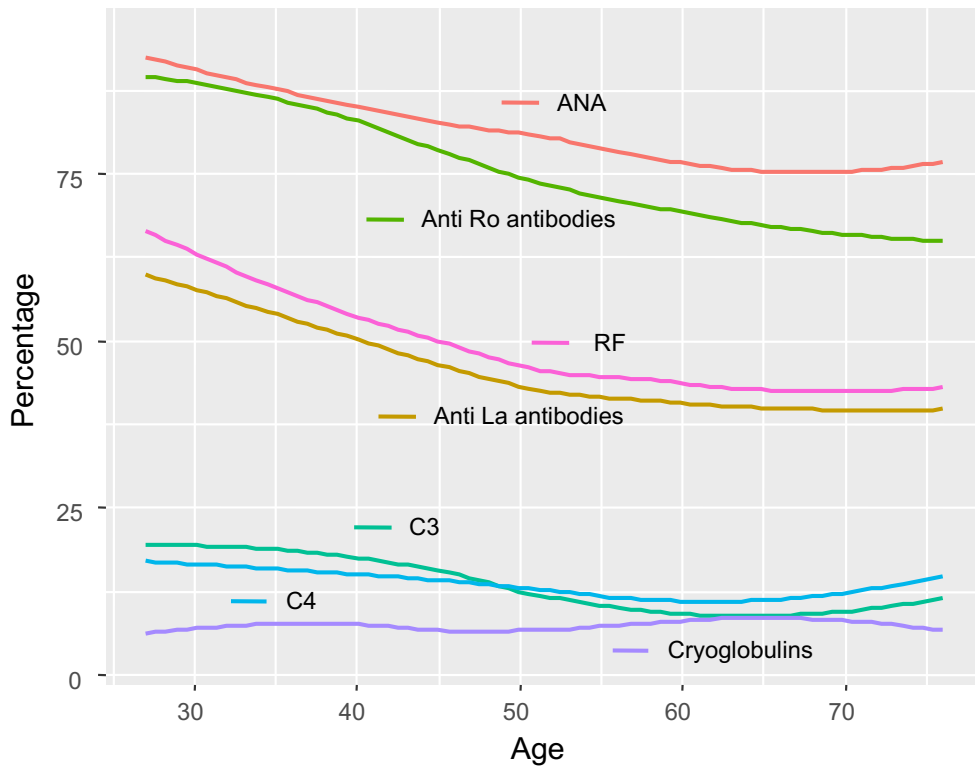
**Figure 2.** Smooth curves (with 95% confidence intervals) representing the association between age at diagnosis and the frequency of autoantibodies and immunological markers at the time of diagnosis.

**Figure 3.** Smooth curves (with 95% confidence intervals) representing the association between age at diagnosis and the frequency of systemic disease (ESSDAI organ-specific domains) at the time of diagnosis.

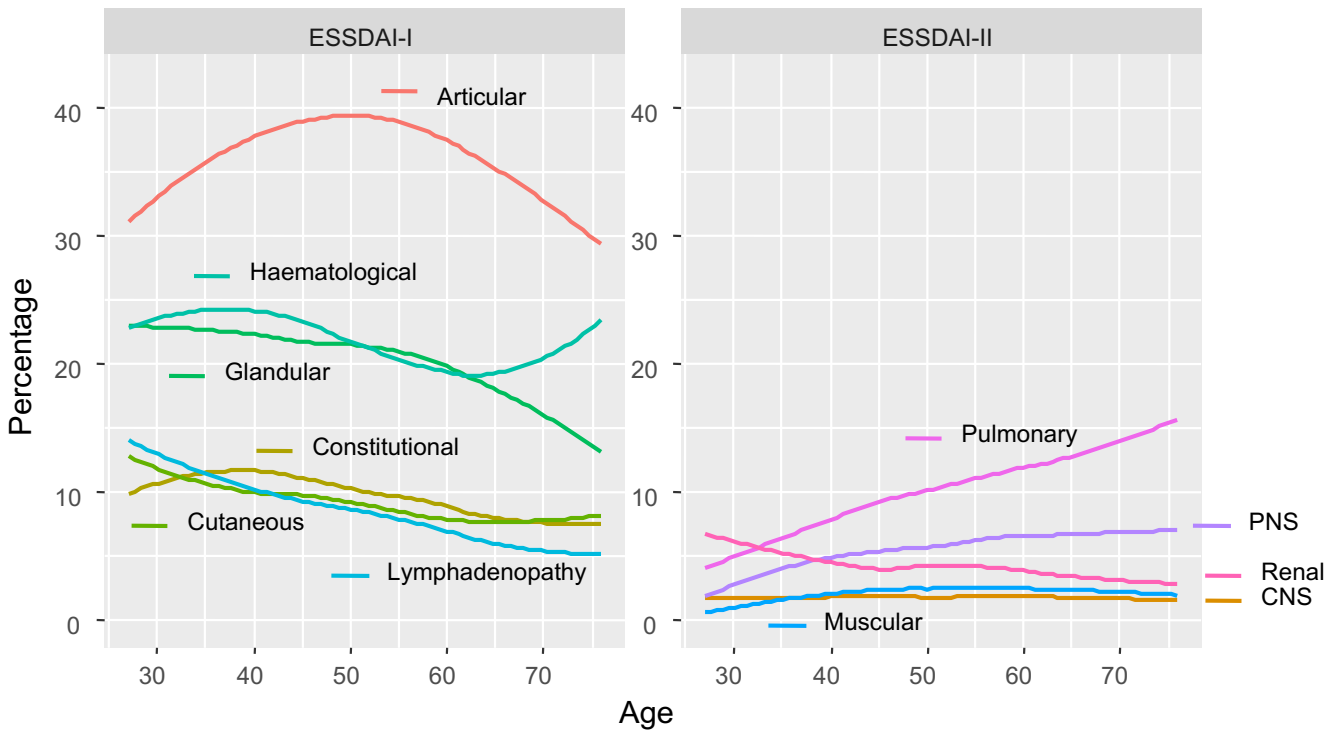
**Figure 1.**



**Figure 2.**



**Figure 3.**



**Table 1.** Baseline characteristics of 12,753 patients with primary Sjögren's Syndrome

| <b>Variable</b>                                    | <b>Patients with pSjS (n = 12,753)</b> |
|--|--|
| Age at diagnosis (n=12,719) (mean $\pm$ SD)        | 52.2 $\pm$ 14.6                        |
| Sex (female)                                       | 11,918 (93.5)                          |
| Ethnicity (n=12,747)                               |  |
| White  | 9,169 (71.9)                           |
| Asian  | 2,059 (16.2)                           |
| Hispanic   | 734 (5.8)                              |
| Black/African-American (AA)                        | 178 (1.4)                              |
| Others   | 607 (4.8)                              |
| Geolocation  |  |
| Europe   | 8,844 (69.3)                           |
| America  | 1,760 (13.8)                           |
| Asia   | 1,880 (14.7)                           |
| Other  | 269 (2.1)                              |
| Signs & symptoms at presentation                   |  |
| Dry eye  | 11,723 (91.9)                          |
| Dry mouth  | 11,891 (93.2)                          |
| Diagnostic tests                                   |  |
| Abnormal ocular tests (any) (n=10,834)             | 9,070 (83.7)                           |
| Schirmer's test (n=10,720)                         | 8,391 (78.3)                           |
| Rose bengal score/other ocular dye score (n=5,103) | 3,643 (71.4)                           |
| Abnormal oral diagnostic tests (any) (n=9,665)     | 7,637 (79.0)                           |
| Unstimulated whole salivary flow (n=7,758)         | 5,908 (76.2)                           |
| Parotid sialography (n=2,416)                      | 1,954 (80.9)                           |
| Salivary scintigraphy (n=2,282)                    | 1,846 (80.9)                           |
| Positive minor salivary gland biopsy(n=9,045)      | 7,431 (82.2)                           |
| Immunological profile                              |  |
| ANA-positive (n=12,020)                            | 9,713 (80.8)                           |
| RF-positive (n=10,424)                             | 5,047 (48.4)                           |
| Positive anti-Ro/La antibodies (n=12,630)          | 9,714 (76.9)                           |
| Anti-Ro antibodies (n=12,624)                      | 9,431 (74.7)                           |
| Anti-La antibodies (n=12,564)                      | 5,641 (44.9)                           |
| Low C3 levels (n=10,392)                           | 1,332 (12.8)                           |
| Low C4 levels (n=10,376)                           | 1,380 (13.3)                           |
| Positive cryoglobulins (n=5,614)                   | 428 (7.6)                              |
| Systemic activity                                  |  |
| Mean ESSDAI score (n=11,724)                       | 5.9 $\pm$ 7.3                          |
| DAS (n=11,724)                                     |  |
| No activity (ESSDAI = 0)                           | 2,239 (19.1)                           |

|                                       |                     |
|---------------------------------------|---------------------|
| Low                                   | 4,471 (38.1)        |
| Moderate                              | 3,604 (30.7)        |
| High                                  | 1,410 (12.0)        |
| ESSDAI domains (score >=1) (n=12,152) |                     |
| Constitutional                        | 1,200 (9.9)         |
| Lymphadenopathy                       | 1,055 (8.7)         |
| Glandular                             | 2,487 (20.5)        |
| Articular                             | 4,493 (37.0)        |
| Cutaneous                             | 1,115 (9.2)         |
| Pulmonary                             | 1,258 (10.4)        |
| Renal                                 | 513 (4.2)           |
| Muscular                              | 262 (2.2)           |
| PNS                                   | 693 (5.7)           |
| CNS                                   | 220 (1.8)           |
| Haematological                        | 2,619/11,986 (21.9) |
| Biological                            | 5,817/11,800 (49.3) |

**Table 2.** Linear regression models fitted to smooth curves to identify linear increasing and decreasing trends.

| Clusters                                   | $\beta$ Coefficient | Std. Error | Sig.   | Adjusted R-squared* |
|--|---------------------|------------|--------|---------------------|
| <b>Glandular component</b>                 |                     |            |        |                     |
| Dry mouth                                  | 0.129               | 0.006      | <0.001 | <b>0.874</b>        |
| Abnormal oral diagnostic tests             | 0.113               | 0.008      | <0.001 | 0.720               |
| Dry eye                                    | 0.110               | 0.012      | <0.001 | 0.513               |
| Abnormal ocular tests                      | 0.080               | 0.009      | <0.001 | 0.528               |
| Positive minor salivary gland biopsy       | -0.080              | 0.008      | <0.001 | 0.547               |
| <b>Immunological component</b>             |                     |            |        |                     |
| Anti-Ro antibodies                         | -0.568              | 0.011      | <0.001 | <b>0.970</b>        |
| RF-positive                                | -0.471              | 0.021      | <0.001 | <b>0.861</b>        |
| Anti-La antibodies                         | -0.424              | 0.018      | <0.001 | <b>0.877</b>        |
| ANA-positive                               | -0.359              | 0.011      | <0.001 | <b>0.927</b>        |
| C3 low                                     | -0.259              | 0.012      | <0.001 | <b>0.846</b>        |
| C4 low                                     | -0.104              | 0.010      | <0.001 | 0.594               |
| Positive cryoglobulins                     | 0.022               | 0.004      | <0.001 | 0.218               |
| <b>Systemic component (ESSDAI domains)</b> |                     |            |        |                     |
| Biological (ESSDAI)                        | -0.435              | 0.019      | <0.001 | <b>0.869</b>        |
| Glandular                                  | -0.179              | 0.008      | <0.001 | <b>0.857</b>        |
| Lymphadenopathy                            | -0.176              | 0.003      | <0.001 | <b>0.977</b>        |
| Constitutional                             | -0.093              | 0.005      | <0.001 | <b>0.812</b>        |
| Cutaneous                                  | -0.093              | 0.004      | <0.001 | <b>0.883</b>        |
| Haematological                             | -0.093              | 0.010      | <0.001 | 0.515               |
| Articular                                  | -0.071              | 0.028      | 0.015  | 0.062               |
| Renal                                      | -0.064              | 0.003      | <0.001 | 0.876               |
| CNS  | -0.002              | 0.001      | <0.001 | 0.139               |

|           |       |       |        |              |
|-----------|-------|-------|--------|--------------|
| Muscular  | 0.022 | 0.003 | <0.001 | 0.405        |
| PNS       | 0.092 | 0.004 | <0.001 | <b>0.881</b> |
| Pulmonary | 0.219 | 0.002 | <0.001 | <b>0.990</b> |

---

Std.: Standard, Sig.: Significance.

\*In bold, smooth curves that best fitted a linear model (adjusted  $R^2 > 0.8$ )

Supplementary Table 1. Main studies focused on characterize young-onset primary SS

| First author | Year | Country | Age criteria | Number of patients | 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%); Xerophtalmia 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 ( $\geq 35$ years), presented a higher prevalence of lymphadenopathy (54% vs 6%, $P<0.001$ , OR 17.9, CI 4.1 $\pm$ 81.8). The prevalence of recurrent parotidomegaly or splenomegaly were also more common in patients with a young onset but NS. Young onset developed |

|      |      |        |            |    |    |    |  |   |  |  |  |   |
|------|------|--------|------------|----|----|----|--|---|--|--|--|---|
|      |      |        |            |    |    |    |  |   |  |  |  | lymphoproliferative disease, compared 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 | Positive biopsy minor salivary glands 80%. The frequency of positive 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 | Raynaud's phenomenon in 50% of ≤45 years compared to 41.2% in ≥45 years; the difference being not NS. Arthritis was 12.5% and 9.8%, respectively (NS). |   |



|                     |      |       |            |     |          |  |   |  |   |  |  |
|---------------------|------|-------|------------|-----|----------|--|---|--|---|--|--|
|                     |      |       |            |     |          |  |   | in young patients.   |   | aged (diagnosed 45 - 60 years) and old patients (≥ 60 years).  |  |
| <b>Ramos-Casals</b> | 2008 | Spain | <35 years  | 137 | NA       | Lower xerostomia compared with those aged >35 years  | 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. | Higher prevalence of vasculitis n= 21(15%) in younger compared with those aged >35 years                                 |
| <b>Botsios</b>      | 2011 | Italy | < 40 years | 130 | 127 (98) | Xerostomia n= 94 (72.3); xerophthalmia n= 102 (78.5). NS between three groups: elderly (> 65 | UWSF (≤1.5mL in 15 minutes) n= 78 (60); salivary sialography (score≥1 | Schirmer I test n= 86 (66.1); Rose-Bengal (score ≥4 ) n= 43 (33.3). NS between three groups: | Focus score ≥1 n= 71 (64.5). NS between three groups: elderly (> 65 | ANA + (titre > 1:80) n= 117 (92.8); Anti-Ro+ n= 109 (83.9); anti-La+ n= 82 (63); RF > 40 IU/L n= 95 (75.8). NS between   | Arthralgia n= 96 (73.9); arthritis n= 48 (36.9); raynaud's phenomenon n= 34 (26.1), lymphadenopathy n=28 (21.5); purpura |

|                 |      |        |            |    |    |  |  |  |  |  |   |
|-----------------|------|--------|------------|----|----|--|--|--|--|--|---|
|                 |      |        |            |    |    | years), adult (> 40 and ≤65 years), and young (≤40 years). | according to Rubin e Holt) n= 88 (67.6). NS between three groups: elderly (> 65 years), adult (> 40 and ≤65 years), and young (≤40 years). | elderly (> 65 years), adult (> 40 and ≤65 years), and young (≤40 years). | years), adult (> 40 and ≤65 years), and young (≤40 years). | three groups: elderly (> 65 years), adult (> 40 and ≤65 years), and young (≤40 years).   | n= 29 (22.3). NS between three groups: elderly (> 65 years), adult (> 40 and ≤65 years), and young (≤40 years). |
| <b>Theander</b> | 2015 | Sweden | < 40 years | 23 | NA | NA   | NA   | NA   | NA   | In 23 patients, primary SS was diagnosed before age 40. These patients showed a significantly higher prevalence of prediagnostic 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=38) | NA  |



|                  |      |       |           |           |          |   |    |    |    |   |   |
|------------------|------|-------|-----------|-----------|----------|---|----|----|----|---|---|
| <b>Zhao</b>      | 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. |
| <b>Nakanishi</b> | 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 | Anti-SSA antibodies and or anti-SSB antibodies n= 82 (94%); ANA > 1/320 n= 30 (39%); RF n=26 (55%). NS compared with < 60 years | 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).  |

|                 |      |             |            |    |           |  |  |   |  |  |  |
|-----------------|------|-------------|------------|----|-----------|--|--|---|--|--|--|
| <b>Anquetil</b> | 2019 | France      | <35 years  | 55 | NA        | Xerostomia 21/55 (38.2) NS;<br>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). | Higher frequency of adenopathy (25.5% vs 11.8%, P = 0.006), purpura (23.6% vs 9.2%, P = 0.002) and renal involvement (16.4% vs 4.4%, P = 0.003) compared with age >35 years. ESSDAI NS at diagnosis. The variation in ESSDAI scores between baseline and the 5-year follow-up was significant (P = 0.005). Significant improvement in ESSDAI scores (-1.27, P<0.001) in the later onset group and a trend for aggravation in the early-onset group (0.72, P = 0.27). |
| <b>Lee</b>      | 2021 | South Korea | < 40 years | 23 | 21 (91.3) | Xerostomia, n (%) 21 (91.3); xerophthalmia, n (%) 17 (73.9) NS between                   | USFR, ml/minute 0.18 (0.03, 0.36); SGUS score ≥ 14 | Abnormal Schirmer's test, n (%) 12 (52.2) NS with elderly group | 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,   | Patients with YopSS had a significantly higher frequency of arthritis (39.1%, 7% and 22.6%,  |

|               |      |       |              |    |         |  |   |    |    |  |   |
|---------------|------|-------|--------------|----|---------|--|---|----|----|--|---|
|               |      |       |              |    |         | EopSS ( $\geq 65$ years), adult-onset (AopSS) ( $\geq 40$ and $< 65$ years), and young-onset (YopSS) ( $< 40$ years).  | was significantly higher in the young (78.3%) ( $P < 0.05$ ) compared with EopSS ( $\geq 65$ years) |    |    | 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.  | respectively, $P < 0.01$ ) than those with EopSS and AopSS.   |
| <b>Alunno</b> | 2021 | Italy | $< 40$ years | 64 | 60 (94) | Xerostomia $< 40$ years $n=56$ (87%) vs $\geq 40$ and $< 65$ $n=142$ (84%) vs Onset $\geq 65$ years $n= 44$ (80%) $p= NS$ . Xerophthalmia $< 40$ years $n=57$ (89%) vs $\geq 40$ and $< 65$ $n=145$ (86%) vs Onset $\geq 65$ years $n= 48$ (87%) $p= NS$ | NA  | NA | NA | Neither anti-Ro nor anti-La $< 40$ years $n= 10$ (16%) vs $\geq 40$ and $< 65$ $n=52$ (31%) vs Onset $\geq 65$ years $n= 28$ (51%) NS; Anti-Ro only $< 40$ years $n= 15$ (23%) vs $\geq 40$ and $< 65$ $n= 63$ (37%) vs $\geq 65$ years $n= 17$ (31%) NS; Anti-La only $< 40$ years $n= 1$ (1.5%) vs $\geq 40$ and $< 65$ $n= 4$ (2%) vs $\geq 65$ years $n= 1$ (2%) NS; both anti-Ro and anti-La $< 40$ | Articular manifestations $n= 32$ (50); purpura $n= 1$ (1.5); raynaud's phenomenon $n=15$ (23); pulmonary manifestations $n= 4$ (6); cardiac manifestations $n= 2$ (3); cutaneous manifestations $n= 5$ (8); PNS manifestations $n= 2$ (3) NS vs $\geq 40$ and $< 65$ ) vs Onset $\geq 65$ years |



|                     |      |        |            |     |    |   |    |    |                           |  |  |
|---------------------|------|--------|------------|-----|----|---|----|----|---------------------------|--|--|
|                     |      |        |            |     |    |   |    |    | compared with Onset <70 y |  |  |
| <b>Tishler</b>      | 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); nti-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)             |
| <b>Ramos-Casals</b> | 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 > 70years compared with those aged < 70 years  | Lower frequency of arthralgia, Raynaud phenomenon and a higher prevalence of pulmonary involvement 26 (17%) were found in patients aged > 70 years compared with those aged < 70 years |



|                |      |         |            |         |            |  |  |  |  |   |   |
|----------------|------|---------|------------|---------|------------|--|--|--|--|---|---|
| <b>Botsios</b> | 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 4mm <sup>2</sup> 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). | ANA n=18 (85.7%); RF n= 15 (71.1%), anti-Ro n= 14 (66.7%), anti-La n= 11 (52.3%). 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 ≤65 years), and young (≤40 years).                                   |
| <b>Chebbi</b>  | 2015 | Tunisie | ≥ 65 years | 18      | 17 (94.5%) | Xerostomia n=18 (100); Xerophthalmia n=18 (100); Keratoconjunctivitis 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   | 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 ≤ 65 years N= 34 (80,9%) p= 0,005, anti-SSA elderly n=6 (33.3%) vs ≤ 65 years N= 29 (69%) p= 0.01 and anti-SSB antibodies elderly n=3                    | Extraglandular 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 |

|                  |      |        |            |          |          |   |  |   |   |   |   |
|------------------|------|--------|------------|----------|----------|---|--|---|---|---|---|
|                  |      |        |            |          |          |   | elderly vs ≤ 65 years  |   |   | (16.6%) vs ≤ 65 years N= 19 (45.2%) p= 0.035 were significantly higher in young subjects  | 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 ≤ 65 years n=6 (14,2%) p=0,019  |
| <b>Nakanishi</b> | 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  | 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) 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. |
| <b>Lacombe</b>   | 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 | Schirmer (mm/5 min) < 50 years n=5 [1–17.3] vs ≥ 50 years n=1 [0–4] < 0.001. Schirmer ≤ | Focus score ≥ 1 on MSGB < 50 years n= 17 (40.5%) vs ≥ 50 years n= 61 (58.1%) p= 0.051 | Anti-SSA antibodies < 50 years n= 9 (21.4%) vs ≥ 50 years n =22 (21.0%) p=0.35; Anti-SSB antibodies < 50 years n= 6               | NA  |

|     |      |             |                 |            |            |  |  |  |   |   |  |
|-----|------|-------------|-----------------|------------|------------|--|--|--|---|---|--|
|     |      |             |                 |            |            |  | diagnostic performances whatever the threshold in the women $\geq$ 50 group.   | 5 mm/5 min < 50 years n 25 (59.5%) vs $\geq$ 50 years n= 90 (85.7%) < 0.001. OSS $\geq$ 5 (if examination was realized) < 50 years n= 2/10 (20.0%) vs $\geq$ 50 years n= 8/29 (27.6%) 0.51 |   | (14.3%) vs $\geq$ 50 years n =16 (15.2%) p=0.95; ANA > 1/200 < 50 years n=12 (28.6%) vs $\geq$ 50 years n = 32 (30.5%) p=0.96 |  |
| Lee | 2021 | South Korea | $\geq$ 65 years | 43 (19.5%) | 40 (93.0%) | Xerostomia, n (%) 40 (93.0) NS with younger group; Xerophthalmia= 35 (81.4) ND. The duration of sicca symptoms in the EopSS ( $\geq$ 65 years) was shorter than in the adult-onset | USFR, ml/minute 0.1 (0, 0.25); SGUS score $\geq$ 14 was significantly lower in the elderly (44.2%) than in the AopSS | Abnormal Schirmer's test, n (%) 25 (58.1) NS between 3 groups  | 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. |

|               |      |       |                 |    |    |  |   |    |    |  |  |
|---------------|------|-------|-----------------|----|----|--|---|----|----|--|--|
|               |      |       |                 |    |    | (AopSS) ( $\geq 40$ and $< 65$ years), ( $P < 0.001$ ) and young-onset (YopSS) ( $< 40$ years) ( $P < 0.05$ ).   | (64.5%) and YopSS (78.3%) ( $P < 0.05$ ) groups |    |    |  | ESSDAI was significantly higher in EopSS than in AopSS (3 vs. 2, $P < 0.01$ ).   |
| <b>Alunno</b> | 2021 | Italy | $\geq 65$ years | 55 | 55 | Xerostomia $< 40$ years $n=56$ (87%) vs $\geq 40$ and $< 65$ $n=142$ (84%) vs Onset $\geq 65$ years $n=44$ (80%) $p= NS$ . Xerophthalmia $< 40$ years $n=57$ (89%) vs $\geq 40$ and $< 65$ $n=145$ (86%) vs Onset $\geq 65$ years $n=48$ (87%) $p= NS$ | NA  | NA | NA | Neither anti-Ro nor anti-La $< 40$ years $n=10$ (16%) vs $\geq 40$ and $< 65$ $n=52$ (31%) vs Onset $\geq 65$ years $n=28$ (51%) NS; Anti-Ro only $< 40$ years $n=15$ (23%) vs $\geq 40$ and $< 65$ $n=63$ (37%) vs $\geq 65$ years $n=17$ (31%) NS; Anti-La only $< 40$ years $n=1$ (1.5%) vs $\geq 40$ and $< 65$ $n=4$ (2%) vs $\geq 65$ years $n=1$ (2%) | Articular manifestations $n=36$ (65); purpura $n=6$ (11); raynaud's phenomenon $n=9$ (14); pulmonary manifestations $n=4$ (7), cardiac manifestations $n=3$ (5), cutaneous manifestations $n=10$ (18), liver manifestations $n=2$ (4); PNS manifestations $n=6$ (11) NS vs $\geq 40$ and $< 65$ ) vs Onset $\geq 65$ years |

