COVID-19 infection in patients with primary Sjögren syndrome: Characterization and outcomes of 51 patients

Pilar Brito-Zerón1,2, Sheila Melchor3, Raphaële Seror4, Roberta Priori5, Roser Solans6, Belchin Kostov7,8, Chiara Baldini9, Francesco Carubbi10, Jose Luis Callejas11, Pablo Guisado-Vasco12, Gabriela Hernández-Molina13, Sandra G. Pasoto14, Valeria Valim15, Antoni Sisó-Almirall7,8,16, Xavier Mariette17, Patricia Carreira3, Manuel Ramos-Casals13,16,18, on behalf of the Sjogren Big Data Consortium.

1Laboratory of Autoimmune Diseases Josep Font, IDIBAPS-CELLEX, Barcelona, Spain.
2Autoimmune Diseases Unit, Department of Medicine, Hospital CIMA- Sanitas, Barcelona, Spain.
3Servicio de Reumatología, Hospital Universitario 12 de Octubre, Madrid, Spain.
4Department of Rheumatology; National Reference Center for Sjögren Syndrome and Rare Autoimmune Diseases, Université Paris-Saclay; Assistance Publique-Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud, AP-HP, Le Kremlin Bicêtre, France.
5Department of Internal Medicine and Medical Specialties, Rheumatology Clinic, Sapienza University of Rome, Rome, Italy.
6Department of Internal Medicine, Hospital Vall d’Hebron, Barcelona, Spain.
7Primary Care Centre Les Corts, Consorci d’Atenció Primària de Salut Barcelona Esquerra (CAPSBE), Barcelona, Spain
8Primary healthcare transversal research group, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain.
9Rheumatology Unit, University of Pisa, Pisa, Italy.
10COVID-19 Medical Unit, San Salvatore Hospital, Department of Medicine, ASL1 Avezzano-Sulmona-L’Aquila, 67100 L’Aquila, Italy.
11Department of Internal Medicine, Hospital San Cecilio, Granada, Spain.
12Department of Internal Medicine, Hospital university quironsalud, Madrid, Spain.
13Immunology and Rheumatology Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. México City, Mexico.
14Rheumatology Division, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil.
15Department of Medicine, Federal University of Espírito Santo, Vitória, Brazil.
16Department of Medicine, Universitat de Barcelona, Barcelona, Spain.
17Center for Immunology of Viral Infections and Autoimmune Diseases, Université Paris-Sud, INSERM UMR1184, Assistance Publique – Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud.
18Department of Autoimmune Diseases, ICMiD, Hospital Clínic, Barcelona, Spain.

*The members of the EULAR-SS Task Force Big Data Consortium who contributed to this study are listed in Appendix 1

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.ub.es

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ABSTRACT

OBJECTIVE. To analyse the prognosis and outcomes of COVID-19 infection in patients with primary Sjögren syndrome (SJS).

METHODS. We searched for patients with primary SJS presenting with COVID-19 infection (defined following according the ECDC guidelines) among those included in the Big Data Sjögren Registry, an international, multicentre registry of patients diagnosed according to the 2002/2016 classification criteria.

RESULTS. 51 patients were included in the study (46 women, mean age at diagnosis of infection of 60 years). According to the number of patients with primary SJS evaluated in the Registry (n=8,211), the estimated frequency of COVID-19 infection was 0.62% (95%CI 0.44 to 0.80). All but two presented with symptoms suggestive of COVID-19 infection, including fever (82%), cough (57%), dyspnea (39%), fatigue/myalgias (27%) and diarrhea (24%), and the most frequent abnormalities included raised LDH (88%), CRP (81%) and D-dimer (82%) values, and lymphopenia (70%). Infection was managed at home in 26 (51%) cases and 25 (49%) required hospitalization (5 required admission to ICU, 4 died). Compared to patients managed at home, those requiring hospitalization had higher odds of having lymphopenia as laboratory abnormality (adjusted OR 21.22, 95%CI 2.39-524.09). Patients with comorbidities had an older age (adjusted OR 1.05, 95% CI 1.00-1.11) and showed a risk for hospital admission 6-times higher than those without (adjusted OR 6.01, 95% CI 1.72-23.51)

CONCLUSION. Baseline comorbidities were a key risk factor for a more complicated COVID-19 infection in patients with primary SJS, with higher rates of hospitalization and poor outcomes in comparison with patients without comorbidities.

KEY WORDS: primary Sjögren syndrome, COVID-19, SARS-Cov-2, comorbidities, outcomes
KEY MESSAGES

What is already known about this subject?
• Nothing. There is no study so far that has evaluated the impact of COVID-19 infection on primary SjS,

What does this study add?
• This is the first study to characterize and evaluate the outcomes of COVID-19 infection in primary SjS
• The estimated frequency of COVID-19 infection in patients with primary SjS was 0.62% (95%CI 0.44 to 0.80).
• Primary SjS-infected individuals seemed to be similarly affected by SARS-CoV-2 compared with the general population in terms of clinical presentation.
• Patients with baseline comorbidities had higher rates of hospitalization and poor outcomes (intensive care admission, death) compared with those without.

How might this impact on clinical practice or future developments?
• These results underscore the need for a specific close monitoring of comorbidities of patients with primary SjS during the pandemic.
INTRODUCTION

Primary Sjögren syndrome (SjS) is a systemic autoimmune disease overwhelmingly diagnosed in women (>95%) aged between 30 and 60-years-old in two thirds of cases [1]. The key clinical feature of primary SjS is the development of sicca symptoms, reported by more than 95% of patients, accompanied in a significant number of cases by a wide variety of systemic manifestations, including the autoimmune damage of internal organs [2]. Primary SjS is not a rare disease, affecting around 1 every 400 people [3].

A novel coronavirus was identified in January 2020, as the etiological agent of a cluster of cases of pneumonia detected in Wuhan City (China). The virus was called “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2) and the lack of prior immunity has resulted in an exponential increase of infected patients across the globe [4], currently with more than 15 million confirmed worldwide cases and more than 600k deaths [5] (July 27, 2020). The disease caused by SARS-CoV-2 has a very wide clinical spectrum ranging from asymptomatic cases [6] to severe acute pneumonia with life-threatening systemic multi-organ failure [7].

People with rheumatic and systemic autoimmune diseases are considered at-risk for a severe coronavirus disease 2019 (COVID-19) considering their underlying abnormal immune response and the frequent use of immunosuppressive drugs. Unfortunately, the body of scientific evidence supporting this potential enhanced risk is small, especially for individual diseases. There is no study so far that has evaluated the impact of COVID-19 infection on primary SjS, which have some specific features that could favouring an increased risk for developing a severe COVID-19 infection (pulmonary autoimmune damage, use of immunosuppressive agents, high frequency of lymphoma) [8–10]. Considering the current progression of the COVID-19 infection, having this information could be useful for planning a personalized medical healthcare to the patient with primary SjS in a pandemic scenario.

The objective of this study is to analyse the prognosis and outcomes of COVID-19 infection in patients with primary SjS.
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 the five continents (see reference 1 for additional methodological details). The centres share a harmonized data infrastructure and conduct cooperative online efforts in order to refine already-collected data in each centre, under the coordination of two data scientists (NAD and BK). Inclusion criteria are the fulfilment of the 2002 classification criteria [11] and/or 2016 ACR/EULAR criteria [12]. Exclusion criteria for considering SjS as a primary disease included chronic HCV/HIV infection, previous lymphoproliferative processes, and associated systemic autoimmune diseases other than SjS. 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 [16]. The study was approved by the Ethics Committee of the Coordinating Centre (Hospital Clinic, Barcelona, Spain, registry HCB/2015/0869).

Design

By the first week of May, all centers included in the Big Data Project were contacted via email by MRC asking for patients included in the Registry who could be diagnosed with COVID-19 infection according to the ECDC guidelines [14] on the basis of epidemiological criteria (having a close contact with a confirmed COVID-19 case in the 14 days prior to onset of symptoms), clinical criteria (fever, cough, shortness of breath, sudden onset of anosmia, ageusia or dysgeusia, headache, chills, muscle pain, fatigue, vomiting and/or diarrhoea), diagnostic criteria (radiological evidence showing lesions compatible with COVID-19) and microbiological criteria (detection of SARS-CoV-2 nucleic acid in a clinical specimen; a positive result in serological tests was also considered as positive criteria). Due to the key role of laboratory parameters in the diagnosis and prognosis of COVID-19 infection [15], we enlarged the diagnostic criteria to include a suggestive biological profile of COVID-19 infection (raised RCP, raised D-dimer, lymphopenia, raised LDH, and/or raised ferritin). According to these criteria, patients were classified according to the following case definitions:

- Possible case: any person meeting the clinical criterion.
- Probable case: any person meeting the epidemiological and clinical criteria, OR any person meeting the enlarged diagnostic criteria (highly suggestive radiological AND biological pictures, after excluding other aetiologies).
- Confirmed case: Any person meeting the microbiological criteria.
Only probable and confirmed cases were included in the study. We excluded patients presenting with suggestive symptoms without any objective test suggesting COVID-19 infection (possible cases), patients in whom the results of the diagnostic tests were not available/reachable (and therefore, case definition cannot be applied), concomitant infectious processes (only for cases lacking a microbiological confirmation of COVID-19 infection), and patients diagnosed as probable cases before March 1st 2020.

Data about COVID-19 infection was retrospectively extracted from electronic health records by use of a standardised de-identified data collection form including demographics, comorbidities (obesity - BMI ≥ 30-, chronic cardiovascular, pulmonary, kidney or hepatic diseases, neoplasia), symptoms at the time of COVID-19 infection diagnosis, COVID-19 pharmacological treatment, and COVID-19 clinical outcomes (including need for hospitalisation/supplemental oxygen, intensive care admission, mechanical ventilation, and death). Clinically, patients with COVID-19 infection were classified as asymptomatic cases (people presenting with no clinical signs and symptoms from medical interviews and physical examinations), mild symptomatic (no need for hospitalisation/supplemental oxygen), and severe symptomatic cases (need for hospitalisation) [16]. Laboratory results were collected as close to the time of SARS-CoV-2 diagnosis or initial hospital admission as possible. When evaluating the use of COVID-19 treatments, hydroxychloroquine, corticosteroids, and tocilizumab were only considered as COVID-19 treatments if they were given for the purpose of COVID-19 treatment. SjS-related features were collected following definitions included in previous studies [1,17,18].

**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 the main features related to COVID-19 infection according to the following dichotomic variables: case classification (confirmed vs probable cases), management of infection (at home vs. hospital admission) and comorbidities (presence vs absence). The t-test was used to compare the mean age at diagnosis. Logistic regression models adjusting for age and sex (as the key prognostic markers for a more complicated COVID-19 infection) were built to confirm the unadjusted univariate results. Logistic multivariate regression models were constructed to analyse independent factors associated with case classification, management of infection and comorbidities. Age, sex and variables with a p < 0.05 in the univariate analysis were included in the models and stepwise model selection by Akaike information criterion (AIC) was used. 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. All analyses
were conducted using the R V.3.5.0 for Windows statistical software package (https://www.R-project.org/).
RESULTS

The email requesting for patients with primary SjS diagnosed with COVID-19 infection was answered by 39 centers (25 did not identify cases and 14 reported 69 potential cases). By June 30, we received the data from 59 cases that were evaluated for inclusion in the study: 6 were excluded after being classified as possible cases and 2 due to lack of accessibility to diagnostic studies in the absence of a confirmed microbiological diagnosis. Therefore, a total of 51 patients were included in the study (46 women, with a mean age at diagnosis of primary SjS of 51.5 years); the frequencies of the main SjS-related features were 94.1% for dry eye, 88.2% for dry mouth, 89.7% for abnormal ocular tests, 76.7% for abnormal oral diagnostic tests, 85.7% for positive minor salivary gland biopsy, 82.3% for anti-Ro antibodies and 35.3% for anti-La antibodies. The mean total ESSDAI score was 7.5 (range 0 to 48). Systemic involvements with the highest frequency of active patients included the articular (52.9%), pulmonary (15.7%) and constitutional (15.7%) ESSDAI domains (Supplementary Table 1). According to the number of patients with primary SjS included by the 39 participating centers (n=8211), the estimated frequency of COVID-19 infection was 0.62% (95%CI 0.44 to 0.80).

Table 1 summarizes the main features of COVID-19 infection in the 51 patients with primary SjS. Patients were diagnosed at a mean age of 60.4 years (range 37 to 88); most were retired, housewife or worked in public services (most as health workers). There were 3 main epidemiological clusters of transmission comprising family, work (mainly in healthcare facilities), and unknown transmission. Comorbidities were reported in 23 (45%) patients, mainly chronic pulmonary diseases, but also chronic cardiovascular diseases and obesity. All patients but two presented with at least one symptom suggestive of COVID-19 infection. The most frequent symptoms were fever (82%), cough (57%), dyspnea (39%), fatigue/myalgias (27%) and diarrhea (24%). According to the microbiological studies, 33 (65%) were classified as confirmed infections (positive PCR result in 31, positive serological studies in 2) and 18 (35%) as probable infections. In 33 patients (24 who required hospitalization and 9 that were visited in the Emergency department and that were discharged under hospital at home supervision), results from laboratory and radiological studies could be collected. Chest radiographs showed no pulmonary opacities (18%), unilateral (12%) or bilateral (70%) airspace opacities. Among laboratory parameters, the most frequent abnormalities included raised LDH (88%), CRP (81%) and D-dimer (82%) values, and lymphopenia (70%) (Table 1).

The disease was managed at home in 26 (51%) cases (close follow-up by GPs or by hospital at home programs) and 25 (49%) required hospitalization. Specific COVID-19 treatment was used in 21 patients, including hydroxychloroquine in 19, ritonavir-boosted lopinavir in 15, azithromycin in 14, pulses of methylprednisolone in 2 and tocilizumab in 2 patients.
Supplemental oxygen was required in 17 (33%) patients. Among the 25 patients who were hospitalized, 5 (20%) required admission to the intensive care unit because of increasing supplemental oxygen requirements, and 2 (8%) required mechanical ventilation. No concomitant bacterial or viral infections were detected during admission (except for one patient who developed pneumococcal pneumonia after being treated with tocilizumab), and 4 patients developed non-infectious complications during the hospitalization (acute kidney failure, pulmonary embolism, post-viral organizing pneumonia and hemophagocytic lymphohistiocytosis -HLH-, respectively). Four patients died 5-10 days after hospital admission (3 due to progressive respiratory failure, one due to HLH). Figure 1 summarizes the individual outcomes of the 51 patients with primary SjS ordered from the youngest to the older age at diagnosis of infection, showing a trend for a progressive increase of hospitalization/ICU requirement as older the patient is, a trend also visible in Figure 2 that stratify the distribution of the main outcomes by age decades.

Demographic, clinical, radiological and laboratory features, and outcomes, were stratified by COVID-19 case definition (probable vs confirmed cases); no statistically-significant differences were observed except for a differentiated contact tracing profile (more patients with no identified positive contact represented in cases classified as probable) and the frequency of general manifestations (higher in probable cases) (Table 2). Stratification according to infection management (hospital admission vs at home) showed that patients who required hospitalisation had a higher frequency of comorbidities (68% vs 23% in those managed at home, p=0.002), respiratory symptoms (80% vs 50%, p=0.04), pulmonary infiltrates (92% vs 56%, p=0.034), lymphopenia (83% vs 33%, p=0.01) in the univariate analysis. Compared to patients managed at home, those requiring hospitalization had higher odds of having comorbidities (adjusted OR 13.28, 95%CI 1.49-326.97) and lymphopenia as laboratory abnormality (adjusted OR 21.22, 95%CI 2.39-524.09) in the logistic multivariate regression model (Table 3). And when patients were stratified according to the presence or absence of baseline comorbidities, a higher mean age (65.8 vs 55.9, p=0.01), a lower frequency of ENT features (9% vs 36%, p=0.044) and a higher frequency in the rates of hospitalization (74% vs 29%, p=0.002), requirement of supplemental oxygen (56% vs 14%, p=0.002) and poor outcomes (26% vs 0%, p=0.006) was found in patients with comorbidities in comparison with those without in the univariate analysis. Patients with comorbidities had an older age (adjusted OR 1.05, 95% CI 1.00-1.11) and showed a risk for requiring hospital admission 6-times higher than those without (adjusted OR 6.01, 95% CI 1.72-23.51) in the logistic multivariate regression model (Table 4).
DISCUSSION

The impact of the COVID-19 pandemic on people with rheumatic and systemic autoimmune diseases has been investigated in several (most retrospective) using various methodological approaches (Supplementary Table 2). Most patients included in these studies have inflammatory arthritis, probably due to their relatively high population frequency (especially for rheumatoid arthritis (RA)) and to the frequent use of biological therapies in these patients. Some studies have reported higher rates of hospitalization [19] or mechanical ventilation [20] in these patients, while in the OPENSAFELY study (the largest cohort study to date analysing clinical risk factors for COVID-19-related death) [21], the age-sex adjusted hazard ratio for death was 1.30 (CI95% 1.21-1.38) for patients with RA, lupus or psoriasis and 2.06 (CI95% 1.62-2.61) for patients with other immunosuppressive conditions. Unfortunately, studies focused on individual systemic autoimmune diseases are very limited and mainly focused on small SLE series of less than 20 patients infected by COVID-19 [22,23]. There is no specific study focused on SjS, with 35 cases (it is unknown whether primary or associated) included in five studies [24–28] but without a specific description of these patients.

In this study, we have tried to capture the broadest, real-life spectrum of COVID-19 infection in primary SjS patients, including not only hospitalized cases, but also patients diagnosed and followed up in a primary care setting. This approach is irretrievably associated with a lower degree of availability of medical examinations performed (laboratory and imaging studies), an aspect that is reflected, for example, in the percentage of cases confirmed by PCR, a test not available at outpatient levels in those countries hardest hit by the pandemic during March-May 2020 and that was usually realized overwhelmingly in severely ill patients. Despite this, we did not find significant differences between patients with or without confirmed infection by virological studies. We have estimated a frequency of COVID-19 infection (including both confirmed and probable cases) of 0.62%, a figure that need to be interpreted cautiously considering the significant risk for bias associated with the very different approaches used to diagnose and follow COVID-19 infection around the world. Until now, only one population-based study carried out in Spain have estimated the prevalence of the infection (PCR+) in SjS, reporting a high figure (1.85%) in comparison with other diseases or with the reference figure [29]. In fact, when we analyse the frequency of PCR+ patients only from the Spanish centers included in our study, the prevalence is 2.3% (33/1438), a very close figure. The reasons explaining why patients with primary SjS may have one of the highest rates of COVID-19 infection (at least in Spain) with respect to other systemic and rheumatic autoimmune diseases are unknown.

The phenotype of COVID-19 infection in our patients with primary SjS (signs and symptoms at presentation, laboratory results, and radiographical abnormalities) is similar to that reported in
the largest reported cohorts of infected patients [30,31], suggesting that primary SjS individuals with COVID-19 could be treated with the standard of care that is being applied for the general population. With respect to the prognosis and outcomes, we found that the main baseline features associated with a more complicated infection were similar to that identified in non-SjS studies [21] including older age, male sex, chronic comorbidities (pulmonary/kidney diseases, hematological neoplasia), pneumonia (respiratory symptoms and pulmonary infiltrates) and lymphopenia. We did not find an association between baseline SjS therapies (hydroxychloroquine, immunosuppressants including corticosteroids and biologics) and hospitalization, probably because of the small sample size. Previous studies in patients with rheumatic diseases have reported an increased odd of hospitalization in patients under corticosteroid therapy, a lower odd in those treated with biologics in monotherapy, and no significant association with the use of antimalarials [28]. With respect to the main outcomes of COVID-19 infection observed in patients with primary SjS, we found that 49% required hospitalization and 33% supplemental oxygen, while among hospitalized patients, 20% required admission to ICU and 8% mechanical ventilation, with an overall mortality rate of 8%. The figures in the largest studies including patients with rheumatic diseases showed very similar figures for hospitalization (44-68%) [19,20,28], need for supplemental oxygen (33%) [20], ICU admission (15-21%) [19,20] and mortality rate (6-9%) [19,20,28]. However, when we stratified the outcomes according to the presence or absence of baseline comorbidities, the figures for poor outcomes were significantly higher (74% for hospitalization rate, 56% for requirement of supplemental oxygen, 24% for ICU admission and 17% for death) in primary SjS patients and concomitant comorbidities. In fact, among patients with primary SjS without baseline comorbidities, none had a poor outcome (0% vs 26% in those with comorbidities), suggesting that the development of a complicated COVID-19 infection seems to be associated more with the existence of pre-infectious comorbidities (most unrelated to the autoimmune disease) than with the primary SjS itself.

The overall body of COVID-19 research may be flawed methodologically and underpinned mainly by uncontrolled confounded evidence [32], in most cases related with the rapid pandemic spread and the lack of a homogeneous protocolized management. This may have a significant impact especially in retrospective, observational studies, and methodological limitations should be well acknowledged and explained. First, a selection bias cannot be discarded in our study, considering the great heterogeneity in the accessibility to the status of infection of all SjS patients among the participating countries, that may be even very different among regions of the same country. The retrospective approach to data collection places limitations on causal conclusions based on the reported results, and the generalizability of our findings may also be
limited because the contribution of few countries and the small number of patients studied. In addition, the small sample size might have generated underpowered statistical tests. Second, the estimation of infection rate is probably biased because local recommendations restricted confirmatory testing. The number of PCR-positive cases might have been underestimated because of the low use of tests, especially at the beginning of the epidemic at for the less severe cases, as has been reported in previous similar studies [33]. As a result, the frequency of primary SjS patients with COVID-19 infection confirmed by PCR we found was lower than that reported in the largest study focused on patients with rheumatic diseases (61% vs 73%) [28]. And third, because of the observational design, individuals were managed from a heterogeneous clinical point of view, and the appropriate diagnostic tests were not carried out in all cases (especially in the less severe clinical cases), biasing the effect of these variables on outcomes. Strengths of the study are the use of the largest international data-sharing registry of primary SjS that has provided the more complete description of the disease in more than 12,000 patients from 20 countries of the five continents [1,17,18], and that all of our cases were resolved or had a known resolution status at the time of manuscript writing, and we gathered complete information on medication use prior to COVID-19 diagnosis and additional historical treatments. As has been advised, principles of open science and raw data sharing may be of greatest importance to allow analysis of data collected during COVID-19 pandemic, especially in patients with very specific disease conditions [34].

To the best of our knowledge, this is the first study to characterize and evaluate the outcomes of COVID-19 infection in patients with primary SjS. Primary SjS-infected individuals seemed to be similarly affected by SARS-CoV-2 compared with the general population in terms of clinical presentation. Notably, baseline comorbidities were risk factors for a more complicated COVID-19 infection in this population, especially chronic pulmonary disease, not only interstitial lung disease (closely related to poor outcome in primary SjS) [35], but also asthma (recently related to a more complicated outcome in COVID-19 infection) [36]. We found that patients with primary SjS and comorbidities had higher rates of hospitalization and poor outcomes (intensive care admission, death) compared with those without baseline comorbidities. These results underscore the need for a specific close monitoring of comorbidities of patients with primary SjS during the pandemic.
REFERENCES


FIGURE LEGENDS

Figure 1. Individual outcomes of the 51 patients with primary SjS ordered from the youngest to the older age at diagnosis of infection. C=cardiovascular disease; P=chronic pulmonary disease; O=Obesity; K=chronic kidney disease; N=neoplasia

Figure 2. Distribution of the main outcomes (at home management, hospitalization, intensive care unit, death) by age decades.
APPENDIX 1

Members of the EULAR-SS Task Force Big Data Consortium who contributed to this study:

P. Brito-Zerón, C. Morcillo (Autoimmune Diseases Unit, Department of Medicine, Hospital CIMA- Sanitas, Barcelona, Spain); P. Brito-Zerón, A. Flores-Chávez, M. Ramos-Casals (Sjögren Syndrome Research Group (AGAUR), Laboratory of Autoimmune Diseases Josep Font, IDIBAPS-CELLEX, Department of Autoimmune Diseases, ICMID, University of Barcelona, Hospital Clinic, Barcelona, Spain); N. Acar-Denizli (Department of Statistics, Faculty of Science and Letters, Mimar Sinan Fine Arts University, Istanbul, Turkey); I.F. Horvath, A. Szanto, T. Tarr (Division of Clinical Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary); R. Seror, X. Mariette (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 Paris, France); T. Mandl, P. Olsson (Department of Rheumatology, Malmö University Hospital, Lund University, Lund, Sweden); X. Li, B. Xu (Department of Rheumatology and Immunology, Anhui Provincial Hospital, China); C. Baldini, S. Bombardieri (Rheumatology Unit, University of Pisa, Pisa, Italy); J.E. Gottenberg (Department of Rheumatology, Strasbourg University Hospital, Université de Strasbourg, CNRS, Strasbourg, France); S. Gandolfo, S De Vita (Clinic of Rheumatology, Department of Medical and Biological Sciences, University Hospital “Santa Maria della Misericordia”, Udine, Italy); R. Priori, F. Giardina (Department of Internal Medicine and Medical Specialties, Rheumatology Clinic, Sapienza University of Rome, Italy); G. Hernandez-Molina, J. Sánchez-Guerrero (Immunology and Rheumatology Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. México City, Mexico); A.A. Kruize, A. Hinrichs (Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands); V. Valim (Department of Medicine, Federal University of Espirito Santo, Vitória, Brazil); D. Isenberg (Centre for Rheumatology, Division of Medicine, University College London, UK); R. Solans (Department of Internal Medicine, Hospital Vall d’Hebron, Barcelona, Spain); M. Rischmueller, S. Downie-Doyle (Department of Rheumatology, School of Medicine, The University of Western Australia, Crawley, Australia); S-K. Kwok, S-H. Park (Department of Rheumatology, Department of Internal Medicine, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea); G. Nordmark (Rheumatology, Department of Medical Sciences, Uppsala University, Uppsala, Sweden); Y. Suzuki, M. Kawano (Division of Rheumatology, Kanazawa University Hospital, Kanazawa, Ishikawa, Japan); R. Giacomelli (Clinical Unit of Rheumatology, University of l’Aquila, School of Medicine, L’Aquila, Italy); V. Devauchelle-Pensec, A. Saraux (Rheumatology Department, Brest University Hospital, Brest, France); B. Hofauer, A. Knopf (Otorhinolaryngology / Head and Neck Surgery, Technical University Munich, Munich, Germany); H. Bootsma, A. Vissink (Department of Rheumatology & Clinical Immunology, University of Groningen, University Medical Center Groningen, the Netherlands); J. Morel (Department of Rheumatology, Teaching hospital and University of Montpellier, Montpellier, France); C. Volleneider (German Hospital, Buenos Aires, Argentina); F. Atzeni (IRCCS Galeazzi Orthopedic Institute, Milan and Rheumatology Unit, University of Messina, Messina, Italy); S. Retamozo (Instituto De Investigaciones En Ciencias De La Salud (INICSA), Universidad Nacional de Córdoba (UNC), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) - Córdoba - Argentina. Instituto Universitario de Ciencias Biomédicas de Córdoba (IUCBC), Córdoba- Argentina); V. Moça Trevisano (Federal University of São Paulo, Sao Paulo, Brazil); B. Armagan, L. Kilic, U. Kalyoncu (Department of Internal Medicine, Hacettepe University, Faculty of Medicine, Ankara, Turkey); S.G. Pasoto (Rheumatology Division, Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil); B. Kostov, A. Sisó-Almirall (Primary Healthcare Transversal Research Group, IDIBAPS, Centre d’Assisténcia Primària ABS Les Corts, CAPSBE, Barcelona, Spain); S. Consani-Fernández (Internal Medicine, Hospital Maciel, Montevideo, Uruguay. Universidad de la República (UdelaR), Montevideo,
Uruguay), S. Melchor, P. Carreira (Servicio de Reumatologia, Hospital Universitario 12 de Octubre, Madrid, Spain), F. Carubbi (COVID-19 Medical Unit, San Salvatore Hospital, Department of Medicine, ASL1 Avezzano-Sulmona-L’Aquila, 67100 L’Aquila, Italy), Jose Luis Callejas (Department of Internal Medicine, Hospital San Cecilio, Granada, Spain), M. López-Dupla (Department of Internal Medicine, Hospital Joan XXIII, Tarragona), R. Pérez-Alvarez (Department of Internal Medicine, Hospital do Meixoeiro, Vigo), M. Akasbi (Department of Internal Medicine, Hospital Infanta Leonor, Madrid), P. Guisado-Vasco (Department of Internal Medicine, Hospital Quirón, Madrid), I. Sánchez (Department of Internal Medicine, Hospital Rey Juan Carlos de Móstoles, Madrid).