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Original article

SARS-CoV-2 infection in patients with primary Sjögren syndrome: characterization and outcomes of 51 patients

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Abstract

Objective. To analyse the prognosis and outcomes of SARS-CoV-2 infection in patients with primary SS.
Methods. We searched for patients with primary SS presenting with SARS-CoV-2 infection (defined following and according to the European Centre for Disease Prevention and Control 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. A total of 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 SS evaluated in the Registry ($n = 8211$), the estimated frequency of SARS-CoV-2 infection was 0.62% (95% CI 0.44, 0.80). All but two presented with symptoms suggestive of COVID-19, including fever (82%), cough (57%), dyspnoea (39%), fatigue/myalgias (27%) and diarrhoea (24%), and the most frequent abnormalities included raised lactate dehydrogenase (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 (five required admission to ICU, four died). Compared with 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 six times higher than those without (adjusted OR 6.01, 95% CI 1.72, 23.51) in the multivariate analysis.
Conclusion. Baseline comorbidities were a key risk factor for a more complicated COVID-19 in patients with primary SS, with higher rates of hospitalization and poor outcomes in comparison with patients without comorbidities.

Key words: Primary SS, COVID-19, SARS-Cov-2, comorbidities, outcomes

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Rheumatology key messages

- The estimated frequency of SARS-CoV-2 infection in patients with primary SS is 0.62%.
- Primary SS patients with COVID-19 and comorbidities had a higher rate of poor outcomes.
- A specific monitoring of comorbidities of patients with primary SS during the pandemic is recommended.

Introduction

Primary SS (SS) is a systemic autoimmune disease overwhelmingly diagnosed in women (>95%) aged between 30 and 60 years in two-thirds of cases [1]. The key clinical feature of primary SS is the development of sicca symptoms, reported by >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 SS is not a rare disease, affecting around one in every 400 people [3].

A novel coronavirus was identified in January 2020, as the aetiological 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 >24 million confirmed worldwide cases and more than 835 000 deaths [5] (14 September 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 on primary SS, which have some specific features that could favour an increased risk for developing a severe COVID-19 (pulmonary autoimmune damage, use of immunosuppressive agents, high frequency of lymphoma) [8–10]. Considering the current progression of the COVID-19, having this information could be useful for planning a personalized medical healthcare to the patient with primary SS in a pandemic scenario.

The objective of this study is to analyse the prognosis and outcomes of COVID-19 in patients with primary SS.

Methods

Patients

The Big Data Sjögren Project Consortium is an international, multicentre registry designed in 2014 to take a 'high-definition' picture of the main features of primary SS using worldwide data-sharing cooperative merging of pre-existing clinical SS databases from leading centres in clinical research in SS from the five continents (see [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 (NA-D and BK). Inclusion criteria are the fulfilment of the 2002 classification criteria [11] and/or 2016 ACR/EULAR criteria [12]. Exclusion criteria for considering SS as a primary disease included chronic HCV/HIV infection, previous lymphoproliferative processes, and associated systemic autoimmune diseases other than SS. Diagnostic tests for SS (ocular tests, oral tests and salivary gland biopsy) were carried out according to the recommendations of the European Community Study Group [13]. 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 centres included in the Big Data Project were contacted via email by MR-C asking for patients included in the Registry who could be diagnosed with COVID-19 according to the European Centre for Disease Prevention and Control 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 [15], we enlarged the diagnostic criteria to include a suggestive biological profile of COVID-19 (raised CRP, raised D-dimer, lymphopenia, raised lactate dehydrogenase (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 (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 1 March 2020.

Data about COVID-19 infection was retrospectively extracted from electronic health records by use of a standardized de-identified data collection form including demographics, comorbidities (obesity (BMI $\geq$30), chronic cardiovascular, pulmonary, kidney or hepatic diseases, neoplasia), symptoms at the time of SARS-CoV-2 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 SARS-CoV-2 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. SS-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 χ^2 test was used to study the main features related to COVID-19 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 multivariate regression models adjusting for age and sex (as the key prognostic markers for a more complicated COVID-19) 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 SS diagnosed with COVID-19 infection was answered by 39 centres (25 did not identify cases and 14 reported 69 potential cases). By 30 June, we received the data from 59 cases that were evaluated for inclusion in the study: six were excluded after being classified as possible cases and two 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 SS of 51.5 years); the frequencies of the main SS-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 0–48). 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 S1, available at *Rheumatology* online). According to the number of patients with primary SS included by the 39 participating centres ($n = 8211$), the estimated frequency of SARS-CoV-2 infection was 0.62% (95% CI 0.44, 0.80).

Table 1 summarizes the main features of SARS-CoV-2 infection in the 51 patients with primary SS. Patients were diagnosed at a mean age of 60.4 years (range 37–88); most were retired, housewives or worked in public services (most as health workers). There were three 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. The most frequent symptoms were fever (82%), cough (57%), dyspnoea (39%), fatigue/myalgias (27%) and diarrhoea (24%). According to the microbiological studies, 33 (65%) were classified as confirmed infections (positive PCR result in 31, positive serological studies in two) 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%)

Table 1 Main features of SARS-CoV-2 infection in the 51 patients with primary SS

		n	%
Age, years (mean, range)	60,35 (37–88)		
Sex	Male	5	9.8
	Female	46	90.2
Country	Spain	33	64.7
	Italy	9	17.6
	France	6	11.8
	Brazil	2	3.9
	Mexico	1	2.0
Current job	Retired	18	35.3
	Public service[a]	14	27.5
	Housewife	8	15.7
	Others	7	13.7
	Unoccupied	2	3.9
	Unknown	1	2.0
Comorbidities	Any	23	45.1
	Cardiovascular disease	8	15.7
	Chronic pulmonary disease	17	33.3
	Obesity (BMI >30)	7	13.7
	Other chronic diseases	4	7.8
Baseline SS-related therapies	Any	30	58.8
	Hydroxychloroquine	19	37.3
	Corticosteroids	9	17.6
	Immunosuppressants/IVIG	9	17.6
	Biological therapies	2	3.9
Positive contact tracing	Family	19	37.3
	Work[b]	14	27.5
	Not identified	18	35.3
Clinical characteristics	Fever (temperature $\geq$37.5°C)	42	82.4
	Cough	29	56.9
	Dyspnoea	20	39.2
	Fatigue/myalgias	14	27.5
	Diarrhoea	12	23.5
	Myalgias	9	17.6
	Anosmia or dysgeusia	8	15.7
	Headache	6	11.8
	Sore throat	3	5.9
	Thoracic pain	3	5.9
	Nausea or vomiting	2	3.9
SARS-CoV-2 infection	PCR+	31	60.8
	Serology+	2	3.9
	Not tested	18	35.3
Radiological features	No infiltrates	6/33	18.2
	Unilateral pulmonary infiltrate	4/33	12.1
	Bilateral pulmonary infiltrates	23/33	69.7
Laboratory parameters	Haemoglobin value <12 g/l	8/33	24.2
	Platelets count $<150\,000/mm^3$	1/33	3.0
	White cells count $<4000/mm^3$	3/33	9.1
	Lymphocytes count $<1000/mm^3$	23/33	69.7
	Raised D Dimer levels	18/22	81.8
	Raised LDH levels	22/25	88.0
	Raised ferritin levels	8/14	57.1
	Raised liver enzymes levels	7/29	24.1
	Raised CRP levels	26/32	81.3
COVID-19 treatment	Any	30	58.8
	Hydroxychloroquine	19	37.3
	Azithromycin	14	27.5
	Ritonavir-boosted lopinavir	15	29.4
	Tocilizumab	2	3.9
	Methylprednisolone	2	3.9
Management	Home	26	51.0

(continued)

Table 1 Continued

		n	%
	Hospitalization	25	49.0
Duration of hospital stay, days	10.8 (1–41)		
Complications during admision	Respiratory failure (suppl O2)	17/25	68.0
	HLH	1/25	4.0
	Pulmonary embolism	1/25	4.0
	Intensive care unit admission	5/25	20.0
	Invasive mechanical ventilation	2/25	8.0
Outcomes	Death	4	7.8
	Recovered	47	92.2

[a]Including healthcare workers ($n = 9$) and other works ($n = 5$). [b]Including working in healthcare facilities ($n = 11$) and others ($n = 3$).

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).

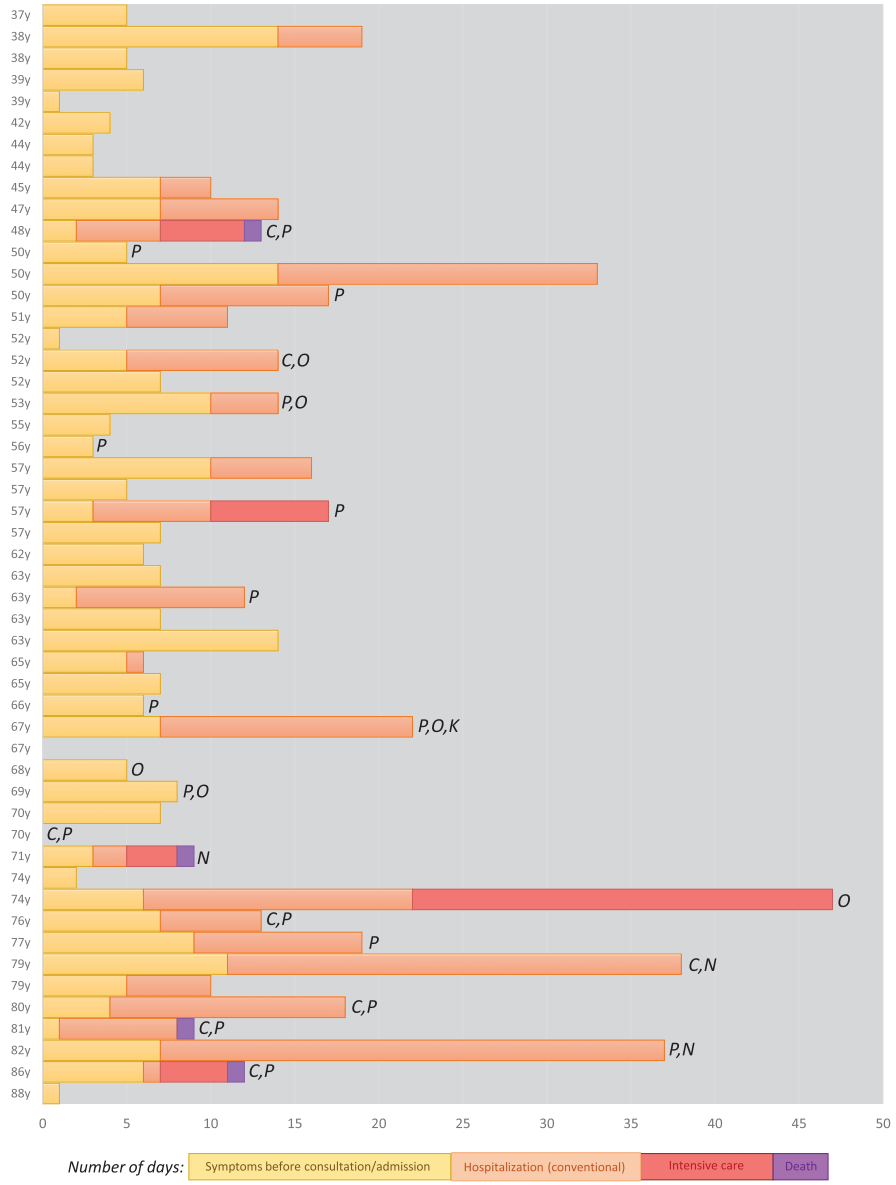
The disease was managed at home in 26 (51%) cases (close follow-up by GPs or by hospital at home programs) and 25 (49%) required hospitalization. Specific COVID-19 treatment was used in 21 patients, including hydroxychloroquine in 19, ritonavir-boosted lopinavir in 15, azithromycin in 14, pulses of methylprednisolone in two and tocilizumab in two patients. Supplemental oxygen was required in 17 (33%) patients. Among the 25 patients who were hospitalized, five (20%) required admission to the intensive care unit because of increasing supplemental oxygen requirements, and two (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 four 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 (three due to progressive respiratory failure, one due to HLH). Figure 1 summarizes the individual outcomes of the 51 patients with primary SS ordered from the youngest to the older age at diagnosis of infection, showing a trend for a progressive increase of hospitalization/ICU requirement the older the patient is, a trend also visible in Fig. 2 that stratifies 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 hospitalization 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 with 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). 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 six 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 S2, available at *Rheumatology* online). 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 (95% CI 1.21, 1.38) for patients with RA, lupus or psoriasis and 2.06 (95% CI 1.62, 2.61) for patients with other immunosuppressive conditions. Unfortunately, studies focused on individual systemic

Fig. 1 Individual outcomes of the 51 patients with primary SS ordered from the youngest to the oldest age at diagnosis of infection



C: cardiovascular disease; K: chronic kidney disease; N: neoplasia; O: obesity; P: chronic pulmonary disease.

autoimmune diseases are very limited and mainly focused on small SLE series of <20 patients infected by SARS-CoV-2 [22, 23]. There is no specific study focused on SS, 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 SARS-CoV-2 infection in primary SS 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 to 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 SARS-CoV-2 infection (including both confirmed and probable cases) of 0.62%, a figure that needs to be interpreted cautiously considering the significant risk for bias associated with the very different approaches used to diagnose and follow SARS-CoV-2 infection around the

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

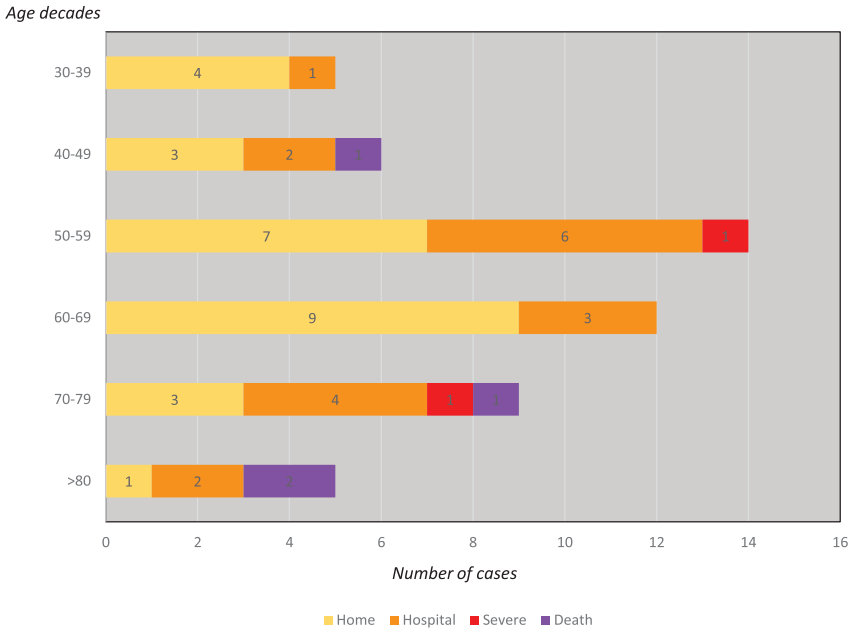


Table 2 Demographic, clinical, radiological and laboratory features, and outcomes stratified by COVID-19 case definition (probable *vs* confirmed cases)

	Probable ($n = 18$)	Confirmed ($n = 33$)	Bilateral *P*-value	Multivariate OR [95% CI]
Sex (men)	1 (5.6)	4 (12.1)	0.645	
Age, mean (S.D.), years	62.5 (13.4)	59.2 (14.1)	0.413	
Comorbidities, any	9 (50)	14 (42.4)	0.769	
Positive contact tracing			0.006	
Family	6 (33.3)	13 (39.4)		Ref
Work	1 (5.6)	13 (39.4)		7.00 [0.87, 152.69]
Not identified	11 (61.1)	7 (21.2)		0.15 [0.02, 0.72]
Baseline therapies			0.644	
None	12 (66.7)	18 (54.5)		
Hydroxychloroquine	1 (5.6)	5 (15.2)		
Immunosuppresants	5 (27.8)	10 (30.3)		
Fever	16 (88.9)	26 (78.8)	0.464	
Respiratory symptoms[a]	13 (72.2)	20 (60.6)	0.543	
Gastrointestinal symptoms[b]	5 (27.8)	9 (27.3)	1.000	
General symptoms[c]	11 (61.1)	10 (30.3)	0.042	0.11 [0.02, 0.53]
ENT symptoms[d]	3 (16.7)	9 (27.3)	0.502	
Chest radiography (infiltrates)	8/10 (80)	19/23 (82.6)	1.000	
Anaemia (Hb $<$ 12 g/L)	3/9 (33.3)	5/24 (20.8)	0.651	
Leukopenia ($<$4000/mm^3)	1/9 (11.1)	2/24 (8.3)	1.000	
Lymphopenia ($<$900/mm^3)	5/9 (55.6)	18/24 (75)	0.400	
Raised D-Dimer levels	6/7 (85.7)	12/15 (80)	1.000	
Raised LDH levels	4/5 (80)	18/20 (90)	0.504	
Raised ferritin levels	3/3 (100)	5/11 (45.5)	0.209	
Raised CRP levels	6/9 (66.7)	20/23 (87)	0.314	
Hospital admission	7 (38.9)	18 (54.5)	0.382	
Supplemental oxygen requirement	3 (16.7)	14 (42.4)	0.073	
Poor outcomes[e]	1 (5.6)	5 (15.2)	0.405	

[a]Cough, dyspnoea, thoracic pain. [b]Diarrhoea, nausea, vomiting. [c]Fatigue, myalgias. [d]Anosmia, dysgeusia, sore throat. [e]Ventilation/ICU requirement, death.

TABLE 3 Demographic, clinical, radiological and laboratory features, and outcomes stratified by SARS-CoV-2 infection management

	At home ($n = 26$)	Hospitalization ($n = 25$)	Bilateral *P*-value	Multivariate OR [95% CI]
Sex (men)	1 (3.8)	4 (16)	0.191	
Age, mean (S.D.), years	56.9 (12.9)	63.9 (14.2)	0.071	
Comorbidities, any	6 (23.1)	17 (68)	0.002	13.28 [1.49, 326.97]
Positive contact tracing			0.064	
Family	8 (30.8)	11 (44)		
Work	7 (26.9)	11 (44)		
Not identified	11 (42.3)	3 (12)		
Baseline therapies			0.919	
None	16 (61.5)	14 (56)		
Hydroxychloroquine	3 (11.5)	3 (12)		
Immunosuppresants	7 (26.9)	8 (32)		
Fever	21 (80.8)	21 (84)	1.000	
Respiratory symptoms[a]	13 (50)	20 (80)	0.040	7.41 [0.87, 96.97]
Gastrointestinal symptoms[b]	8 (30.8)	6 (24)	0.755	
General symptoms[c]	13 (50)	8 (32)	0.258	
ENT symptoms[d]	10 (38.5)	2 (8)	0.019	
COVID-19 definition (confirmed)	15 (57.7)	18 (72)	0.382	
Chest radiography (infiltrates)	5/9 (55.6)	22/24 (91.7)	0.034	
Anaemia (Hb $<$ 12 g/L)	1/9 (11.1)	7/24 (29.2)	0.394	
Leukopenia ($<$4000/mm^3)	0/9 0	3/24 (12.5)	0.545	
Lymphopenia ($<$900/mm^3)	3/9 (33.3)	20/24 (83.3)	0.010	21.22 [2.39, 524.09]
Raised D-Dimer levels	3/3 (100)	15/19 (78.9)	1.000	
Raised LDH levels	3/4 (75)	19/21 (90.5)	0.422	
Raised ferritin levels	1/2 (50)	7/12 (58.3)	1.000	
Raised CRP levels	6/8 (75)	20/24 (83.3)	0.625	
Supplemental oxygen requirement	1 (3.8)	16 (64)	$<$0.001	
Poor outcomes[e]	0 0	6 (24)	0.010	

[a]Cough, dyspnoea, thoracic pain. [b]Diarrhoea, nausea, vomiting. [c]Fatigue, myalgias. [d]Anosmia, dysgeusia, sore throat. [e]Ventilation/ICU requirement, death.

world. Despite this limitation, the estimated infection rate in patients with primary SS is too close to the infection rate estimated by the WHO in the Spanish general population during the same study period (0.53%, 95% CI 0.50, 0.56) [5]. Until now, only one population-based study carried out in Spain has estimated the prevalence of the infection (PCR+) in SS, 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 from only the Spanish centres included in our study, the prevalence is 2.3% (33/1438), a very close figure. The reasons explaining why patients with primary SS may have one of the highest rates of SARS-CoV-2 infection (at least in Spain) with respect to other systemic and rheumatic autoimmune diseases are unknown.

The phenotype of SARS-CoV-2 infection in our patients with primary SS (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 SS 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-SS 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 SS therapies and hospitalization, probably because of the small sample size. Previous studies in patients with rheumatic diseases have reported increased odds of hospitalization in patients under corticosteroid therapy, lower odds in those treated with biologics in monotherapy, and no significant association with the use of antimalarials [28]. According to a recently published study by Sisó-Almirall *et al.* [32], autoimmune diseases were an independent risk factor for ICU admission and death.

With respect to the main outcomes of SARS-CoV-2 infection, the figures observed in our patients with primary SS were similar to that reported in patients with rheumatic diseases 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], and also similar to the figures recently reported in

TABLE 4 Demographic, clinical, radiological and laboratory features, and outcomes stratified according to the presence or absence of comorbidities

	No comorbidities ($n = 28$)	Comorbidities ($n = 23$)	Bilateral *P*-value	Multivariate OR [95% CI]
Sex (men)	1 (3.6)	4 (17.4)	0.162	
Age, mean (S.D.), years	55.9 (13)	65.8 (13.1)	0.010	1.05 [1.00, 1.11]
Positive contact tracing			0.084	
Family	10 (35.7)	9 (39.1)		
Work	11 (39.3)	3 (13)		
Not identified	7 (25)	11 (47.8)		
Baseline therapies			0.211	
None	17 (60.7)	13 (56.5)		
Hydroxychloroquine	5 (17.9)	1 (4.3)		
Immunosuppresants	6 (21.4)	9 (39.1)		
Fever	23 (82.1)	19 (82.6)	1.000	
Respiratory symptoms[a]	18 (64.3)	15 (65.2)	1.000	
Gastrointestinal symptoms[b]	7 (25)	7 (30.4)	0.757	
General symptoms[c]	11 (39.3)	10 (43.5)	0.783	
ENT symptoms[d]	10 (35.7)	2 (8.7)	0.044	
COVID-19 definition (confirmed)	19 (67.9)	14 (60.9)	0.769	
Chest radiography (infiltrates)	10 (71.4)	17 (89.5)	0.363	
Anaemia (Hb $<$ 12 g/L)	4 (30.8)	4 (20)	0.681	
Leukopenia ($<$4000/mm^3)	0 (0)	3 (15)	0.261	
Lymphopenia ($<$900/mm^3)	9 (69.2)	14 (70)	1.000	
Raised D-Dimer levels	7 (87.5)	11 (78.6)	1.000	
Raised LDH levels	7 (77.8)	15 (93.8)	0.530	
Raised ferritin levels	3 (60)	5 (55.6)	1.000	
Raised CRP levels	9 (75)	17 (85)	0.647	
Hospital admission	8 (28.6)	17 (73.9)	0.002	6.01 [1.72, 23.51]
Supplemental oxygen requirement	4 (14.3)	13 (56.5)	0.002	
Poor outcomes[e]	0 (0)	6 (26.1)	0.006	

[a]Cough, dyspnoea, thoracic pain. [b]Diarrhoea, nausea, vomiting. [c]Fatigue, myalgias. [d]Anosmia, dysgeusia, sore throat. [e]Ventilation/ICU requirement, death.

the Spanish general population (hospitalization rate of 49.1% and mortality rate of 5.6%, respectively) [32]. However, when we stratified the outcomes according to the presence or absence of baseline comorbidities, the figures for poor outcomes were significantly higher in primary SS patients and concomitant comorbidities. In fact, among patients with primary SS without baseline comorbidities, none had a poor outcome, suggesting that the development of a complicated COVID-19 seems to be associated more with the existence of pre-infectious comorbidities (most unrelated to the autoimmune disease) than with the primary SS itself.

The overall body of COVID-19 research may be flawed methodologically and underpinned mainly by uncontrolled confounded evidence [33], 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 SS 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 of 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 for the less severe cases, as has been reported in previous similar studies [34]. As a result, the frequency of primary SS patients with SARS-CoV-2 infection confirmed by PCR we found was lower than that reported in the largest study focused on patients with rheumatic diseases [28].

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 SS that has provided the more complete description of the disease in >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 the COVID-19 pandemic, especially in patients with very specific disease conditions [35].

To the best of our knowledge, this is the first study to characterize and evaluate the outcomes of SARS-CoV-2 infection in patients with primary SS. Primary SS-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 in this population, especially chronic pulmonary disease, not only interstitial lung disease (closely related to poor outcome in primary SS) [36], but also asthma (recently related to a more complicated outcome in SARS-CoV-2 infection) [37]. We found that patients with primary SS 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 SS during the pandemic.

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Data availability statement

External investigators interested in collaboration or using the data from the Sjögren Big Data Project can contact Dr Manuel Ramos-Casals (mramos@clinic.cat). Requests will be considered on a case-by-case basis.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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