Post-COVID-19 syndrome in patients with primary Sjögren's syndrome after acute SARS-CoV-2 infection

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on behalf of the Sjögren Big Data Consortium

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Received on June 17, 2021; accepted in revised form on August 30, 2021.

Clin Exp Rheumatol 2021; 39 (Suppl. 133): S57-S65.

Key words: primary Sjögren syndrome, post-COVID-19 syndrome, SARS-CoV-2, long COVID-19, hydroxychloroquine, hospital admission

Competing interests: page S-64.

ABSTRACT

Objective. *To analyse the frequency and characteristics of post-COVID-19 syndrome in patients with primary Sjögren's syndrome (pSS) affected by acute SARS-CoV-2 infection.*

Methods. *By the first week of April 2021, all centres included in the Big Data Sjögren Consortium were contacted asking for patients included in the Registry diagnosed with SARS-CoV-2 infection according to the ECDC guidelines. According to the NICE definitions, symptoms related to COVID-19 were classified as acute COVID-19 (signs and symptoms for up to 4 weeks), ongoing symptomatic COVID-19 (presence of signs and symptoms from 4 to 12 weeks) and post-COVID-19 syndrome (signs and symptoms that continue for >12 weeks not explained by an alternative diagnosis after a protocolised study).*

Results. *We identified 132 patients who were followed a mean follow-up of 137.8 days (ranging from 5 days to 388 days) after being diagnosed with COVID-19. In the last visit, 75 (57%) patients remained symptomatic: 68 (52%) remained symptomatic for more than 4 weeks fulfilling the NICE definition for ongoing symptomatic post-COVID-19, and 38 (29%) remained symptomatic for more than 12 weeks fulfilling the definition of post-COVID-19 syndrome. More than 40% of pSS patients reported the persistence of four symptoms or more, including anxiety/depression (59%), arthralgias (56%), sleep disorder (44%), fatigue (40%), anosmia (34%) and myalgias (32%). Age-sex adjusted multivariate analysis identified raised LDH levels (OR 10.36), raised CRP levels (OR 7.33), use of hydroxychloroquine (OR 3.51) and antiviral agents (OR 3.38), hospital admission (OR 8.29), mean length of hospital admission (OR 1.1) and requirement of supplemental oxygen (OR 6.94) as factors associated with a higher risk of developing post-COVID-19 syndrome. A sensitivity analysis including hospital admission in the adjusted model confirmed raised CRP levels (OR 8.6, 95% CI 1.33–104.44) and use of hydroxychloroquine (OR 2.52, 95% CI 1.00–6.47) as the key independent factors associated with an enhanced risk of developing post-COVID-19 syndrome.*

Conclusion. *This is the first study that analyses the frequency and characteristics of post-COVID-19 syndrome in patients affected by a systemic autoimmune disease. We found that 57% of patients with pSS affected by COVID-19 remain symptomatic after a mean follow-up of 5 months. The risk of developing post-COVID-19 syndrome in patients who required hospitalisation was 8-times higher than in non-hospitalised patients, with baseline raised CRP levels and the use of hydroxychloroquine being independent risk factors for post-COVID-19.*

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease overwhelmingly diagnosed in women (>95%), in two-thirds of cases aged between 30 and 60 years old (1). Immune-mediated inflammation of the exocrine glands causes secretory gland dysfunction, leading to dryness of the main mucosal surfaces. Sicca symptoms are accompanied in a significant

number of cases by a wide variety of systemic manifestations, including the autoimmune damage of internal organs (2). Therefore, SS is a serious disease, with a substantial impact on the quality of life (QoL) (3), the development of organ-specific damage that may end in chronic failure of internal organs, and a high risk of development of haematological cancer (4).

COVID-19 is an infectious disease caused by a novel coronavirus identified at the end of 2019 that was named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) that is most commonly spread via respiratory route after a close person to person contact (5). The disease was declared a pandemic by the WHO on March 11, 2020, and has a very wide clinical spectrum, ranging from asymptomatic cases (accounting for a substantial proportion of infections) to severe infections consisting of bilateral pneumonia that, in some cases, may progress to respiratory failure, multi-organ failure, and death (6,7). Several studies have identified baseline features related to a poor prognosis, including some epidemiological (male gender, older age, non-White people) and clinical (comorbidities) features (8). Patients with systemic autoimmune diseases have an increased risk of having a worse evolution of SARS-CoV-2 infection and are considered as a high-risk group for developing a more complicated COVID-19 (9).

Similar to other post-acute viral syndromes, there are increasing reports of prolonged or persistent symptoms after acute COVID-19 (10). Recently, the National Institute for Health and Care Excellence (NICE) guidelines have defined post-COVID-19 syndrome as the persistence for >12 weeks of those signs and symptoms developed during the acute infection, without a reasonable explanation by an alternative diagnosis (11). Recently-published guidelines focused on the management of long COVID-19 in a primary care setting have also endorsed the use of these terms and definitions recommended by the NICE (12).

Very few studies have analysed the impact of SARS-CoV-2 infection in patients with pSS (13-15), and none has evaluated the development of the post-COVID-19 syndrome. The objective of this study was to analyse the frequency and characteristics of the post-COVID-19 syndrome in patients with pSS affected by acute SARS-CoV-2 infection.

Methods

Patients

The Big Data Sjögren Consortium is an international, multicentre registry designed in 2014 to take a "high-definition" picture of the main features of pSS using a worldwide data-sharing cooperative merging of pre-existing clinical SS databases from leading centres in clinical research in SS from the five continents (see reference 1 for additional methodological details). Inclusion criteria are the fulfilment of the 2002 classification criteria (16), and since 2017, patients were evaluated according to the 2016 ACR/EULAR criteria (17).

Design

By the first week of April 2021, all centres included in the Big Data Consortium were contacted via email by MRC asking for patients included in the Registry diagnosed with SARS-CoV-2 infection defined according to the ECDC guidelines (18). Only probable and confirmed ECDC cases were included in the study. We excluded patients presenting with suggestive symptoms without any objective test suggesting COVID-19 infection, patients in whom the results of the diagnostic tests were not available/reachable (and therefore, case definition cannot be applied), and those with concomitant infectious processes at the time of SARS-CoV-2 infection diagnosis. Data about COVID-19 infection were retrospectively extracted from electronic health records by use of a standardised de-identified data collection form described in a previous manuscript (15). At the last visit of follow-up after the diagnosis of SARS-CoV-2 infection, patients were asked by the physician in charge about the presence or absence of the main symptoms related to SARS-CoV-2 infection (12). Symptoms were clustered following an organ-specific classification into 6 main categories (general, respiratory, musculoskeletal, ear-nose-throat (ENT), digestive and neurological symptoms). We used the following NICE definitions based on the effects of COVID-19 at different time points (11): acute COVID-19 (signs and symptoms for up to 4 weeks), ongoing symptomatic COVID-19 (presence of signs and symptoms from 4 to 12 weeks) and post-COVID-19 syndrome (signs and symptoms that continue for > 12 weeks not explained by an alternative diagnosis after a protocolised study) (11).

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 acute SARS-CoV-2 infection. The t-test was used to compare the mean age at diagnosis and duration of the hospital discharge. Logistic multivariate regression models adjusting for age and sex (the key prognostic markers for a more complicated COVID-19 infection) were constructed to analyse independent factors associated with the fulfilment of criteria of post-COVID-19 syndrome at the last visit in comparison with patients who were asymptomatic. A sensitivity analysis was performed considering logistic multivariate regression models adjusted for age, sex and hospital admission. Heat maps were used to identify patterns about the frequency of the main symptoms reported at the time of diagnosis of acute infection, and how the frequency varied in the last visit of follow-up. 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

We identified 162 patients with pSS and SARS-CoV-2 infection in the Big Data Sjögren Cohort. After excluding asymptomatic patients, those who died and patients lacking a follow-up (Supplementary Fig. S1), we finally selected

132 patients who were followed after being diagnosed with COVID-19 (Table I). There were 126 women and 6 men, with a mean age of 54.8 years; the frequencies of the main SS-related features were 94.7% for dry eye, 93.2% for dry mouth, 79.1% for abnormal ocular tests, 69.2% for abnormal oral diagnostic tests, 90.1% for positive minor salivary gland biopsy, 79.1% for anti-Ro antibodies and 40.5% for anti-La antibodies.

Characterisation of COVID-19

Table I summarises the main baseline features of patients with pSS at the time of being diagnosed with COVID-19. Comorbidities were reported in 69 (52%) patients, mainly hypertension, chronic pulmonary disease, and obesity. According to the microbiological studies, 114 (86%) were classified as confirmed infections (positive PCR result in 109, positive serological studies in 5) and 18 (14%) as probable infections. In 70 patients, results from radiological studies could be collected. Chest radiographs showed no pulmonary opacities (39%), unilateral (10%) or bilateral (51%) airspace opacities. The disease was managed at home in 98 (74%) cases (close follow-up by GPs or by hospital at home programs), and the remaining 34 (26%) patients required hospitalisation. Among the 34 patients who were hospitalised, 21 (62%) required supplemental oxygen, and 3 (9%) required non-invasive or invasive ventilation. The main symptoms related to acute SARS-CoV-2 infection are summarised in Table II.

Figure 1A summarises the frequency of symptoms related to acute SARS-CoV-2 infection in the entire cohort and the separated frequencies reported by patients managed at home and by those who required hospital admission.

Symptoms of COVID-19 at the last visit

After a mean follow-up of 137.8 days (ranging from 5 days to 388 days), 57 (43%) patients were asymptomatic (recovered patients), and 75 (57%) remained symptomatic at the last visit of follow-up; 18 patients reported one symptom, 15 two, 11 three and 31 four symptoms or more.

Table I. Main features of COVID-19 in 132 patients with pSS.

Variable	n	%
Age, years (mean ± SD)	54.8 ± 13.9	
Sex		
Male	6	4.5
Female	126	95.5
Country		
Spain	33	25.0
Turkey	20	15.2
Italy	20	15.2
France	9	6.8
Brazil	18	13.6
Portugal	16	12.1
Others	16	12.1
Comorbidities		
Any	69	52.3
Cardiovascular disease	15	11.4
Pulmonary disease	24	18.2
Smoking (past/active)	23	17.4
Hypertension	38	28.8
Diabetes Mellitus	9	6.8
Obesity	18	13.6
Cancer history	8	6.1
Renal failure	2	1.5
Sjögren's criteria		
Dry eye	125	94.7
Dry mouth	123	93.2
Positive ocular tests	87/110	79.1
Positive oral tests	45/65	69.2
Salivary gland biopsy (positive)	82/91	90.1
Ro antibodies	102/129	79.1
La antibodies	51/126	40.5
Baseline SS-related therapies		
Any	82	62.1
Hydroxychloroquine	56	42.4
Corticosteroids	31	23.5
Immunosuppressants	32	24.2
Biological therapies	11	8.3
Positive contact tracing		
Family	51	38.6
Work (b)	13	9.8
Social	7	5.3
School	1	0.8
Healthcare	10	7.6
Not identified	50	37.9
COVID diagnosis confirmation		
PCR+	109	82.6
Serology+	5	3.8
Not tested	18	13.6
Fever (≥ 38ºC)	49/90	54.4
Respiratory rate (≥ 20BPM)	27/61	44.3
Baseline O2 saturation (%)		
≤95%	33/83	39.8
≤90%	13/83	15.7
Radiological features		
No infiltrates	27/70	38.6
Unilateral pulmonary infiltrate	7/70	10.0
Bilateral pulmonary infiltrates	36/70	51.4
Laboratory parameters		
Haemoglobin value <12 g/l	13/68	19.1
Platelets count <150000/mm3	3/68	4.4
White cells count <4000/mm3	6/67	9.0
Lymphocytes count <1000/mm3	36/66	54.5
Raised D Dimer levels	32/51	62.7
Raised LDH levels	30/55	54.5
Raised ferritin levels	18/40	45.0
Raised liver enzymes levels	10/62	16.1
Raised CRP levels	48/66	72.7
COVID-19 treatment		
Hydroxychloroquine	61	46.2
Azithromycin	34	25.8
Oral prednisone	36	27.3
Intravenous methylprednisolone	10	7.6
Antiviral agents	25	18.9
Tocilizumab	2	1.5
Management		
Home	98	74.2
Hospital admission	34	25.8
Hospital discharge days after covid dx (mean ± SD)	3.2 ± 7.6	
Complications during admission		
Supplemental oxygen	21/34	61.8
Non-invasive ventilation	3/34	8.8
Invasive ventilation	1/34	2.9

Table II summarises the frequency of individual and clustered symptoms at the time of acute infection and at the last visit of follow-up, differentiating between persistent and new symptoms. Among the most frequently reported persistent symptoms, the highest frequencies were reported for anxiety/depression (59%), arthralgias (56%), sleep disorder (44%), fatigue (40%), anosmia (34%) and myalgias (32%). Persistent symptoms were clustered as neuropsychological (47%), musculoskeletal (40%), general (34%), ENT (34%), respiratory (31%) and digestive (11%) symptoms. In addition, 12 patients developed new symptoms (not reported during the acute infection); the most common were fatigue (n=6), memory loss (n=5), anxiety/depression (n=5), arthralgias (n=4), weight loss (n=3) and sleep disorder (n=3).

Figure 1B summarises the frequency of symptoms reported by the patients at the last visit in the entire cohort and the separated frequencies reported by patients who were managed at home and by those who required hospital admission.

Post-COVID-19 syndrome

Among the 75 patients who remained symptomatic at the last follow-up visit, 68 had a follow-up higher than 4 weeks fulfilling the NICE definition for ongoing symptomatic COVID-19, and 38 had a follow-up higher than 12 weeks fulfilling the NICE definition of post-COVID-19 syndrome (Suppl. Fig. S1). We analysed the predictive value of baseline features at the time of acute infection for the development of post-COVID-19 syndrome (Suppl. Table S1). Age-sex adjusted multivariate analysis identified raised LDH levels (OR 10.36, 95% CI 1.97–79.56), raised CRP levels (OR 7.33, 95% CI 1.52–56.82), use of hydroxychloroquine (OR 3.51, 95% CI 1.50–8.55) and antiviral agents (OR 3.38, 95% CI 1.26–9.65), hospital admission (OR 8.29, 95% CI 2.74–29.21), mean length of hospital admission (OR 1.1, 95% CI 1.03-1.2) and requirement of supplemental oxygen (OR 6.94, 95% CI 2.03–29.02) as factors associated with a higher risk of developing post-COVID-19 syndrome (Suppl. Table S1). Among SS diagnostic criteria and

Table II. Symptoms related to acute COVID-19, active symptoms reported at the last visit, persistent symptoms and new symptoms at the last visit.

	Acute SARS-CoV-2 infection N (%)	Active symptoms at the last visit n (%)	Persistent symptoms at the last visit n/N (%)	New symptoms at the last visit* new/n (%)
Total features (any)	132 (100)	75 (56.8)	75/132 (56.8)	None
Respiratory features (any)	87 (65.9)	29 (22)	27/87 (31)	2/29 (6.9)
Cough	75 (56.8)	14 (10.6)	13/75 (17.3)	1/14 (7.1)
Dyspnoea	49 (37.1)	13 (9.8)	13/49 (26.5)	None
Expectoration sputum production	11 (8.3)	4 (3)	2/11 (18.2)	2/4 (50)
Chest pain	26 (19.7)	6 (4.5)	4/26 (15.4)	2/6 (33.3)
General features (any)	113 (85.6)	42 (31.8)	39/113 (34.5)	3/42 (7.1)
Fever	69 (52.3)	1 (0.8)	1/69 (1.4)	None
Fatigue	91 (68.9)	42 (31.8)	36/91 (39.6)	6/42 (14.3)
Chills	26 (19.7)	3 (2.3)	3/26 (11.5)	None
Wheezing	8 (6.1)	0 (0)	0/8 (0)	None
Syncope	4 (3)	1 (0.8)	0/4 (0)	1/1 (100)
Bloating	3 (2.3)	0 (0)	0/3 (0)	None
Musculoskeletal features (any)	75 (56.8)	33 (25)	30/75 (40)	3/33 (9.1)
Myalgias	72 (54.5)	25 (18.9)	23/72 (31.9)	2/25 (8)
Arthralgias	50 (37.9)	32 (24.2)	28/50 (56)	4/32 (12.5)
ENT features (any)	84 (63.6)	30 (22.7)	29/84 (34.5)	1/30 (3.3)
Sore throat	40 (30.3)	9 (6.8)	8/40 (20)	1/9 (11.1)
Dysgeusia	54 (40.9)	16 (12.1)	16/54 (29.6)	None
Anosmia	59 (44.7)	20 (15.2)	20/59 (33.9)	None
Runny nose	26 (19.7)	6 (4.5)	4/26 (15.4)	2/6 (33.3)
Haemoptysis	4 (3)	0 (0)	0/4 (0)	None
Ear pain	10 (7.6)	3 (2.3)	3/10 (30)	None
Digestive features (any)	73 (55.3)	10 (7.6)	8/73 (11)	2/10 (20)
Anorexia lack of appetite	45 (34.1)	5 (3.8)	5/45 (11.1)	None
Diarrhoea	39 (29.5)	1 (0.8)	1/39 (2.6)	None
Nausea	29 (22)	2 (1.5)	2/29 (6.9)	None
Vomiting	9 (6.8)	0 (0)	0/9 (0)	None
Weight loss	23 (17.4)	4 (3)	1/23 (4.3)	3/4 (75)
Abdominal pain	22 (16.7)	5 (3.8)	3/22 (13.6)	2/5 (40)
Neurological features (any)	72 (54.5)	37 (28)	34/72 (47.2)	3/37 (8.1)
Altered consciousness confusion	9 (6.8)	1 (0.8)	0/9 (0)	1/1 (100)
Headache	59 (44.7)	14 (10.6)	14/59 (23.7)	None
Attention disorder	13 (9.8)	10 (7.6)	8/13 (61.5)	2/10 (20)
Memory loss	8 (6.1)	11 (8.3)	6/8 (75)	5/11 (45.5)
Anxiety depression	27 (20.5)	21 (15.9)	16/27 (59.3)	5/21 (23.8)
Sleep disorder	27 (20.5)	15 (11.4)	12/27 (44.4)	3/15 (20)
Conjunctivitis red eyes	11 (8.3)	5 (3.8)	5/11 (45.5)	None
Hair loss	8 (6.1)	8 (6.1)	7/8 (87.5)	1/8 (12.5)

*Symptoms that were not present at the time of acute infection.

related therapies, underlying treatment with hydroxychloroquine was associated with a higher risk of developing post-COVID-19 syndrome, although there were no statistically-significant differences in the adjusted model (Suppl. Table S2). As most risk factors were linked to hospital admission, we carried out a sensitivity analysis including hospital admission in the adjusted model, confirming raised CRP levels (OR 8.6, 95% CI 1.33–104.44) and use of hydroxychloroquine (OR 2.52, 95% CI 1.00–6.47) as independent factors associated with an enhanced risk of developing post-COVID-19 syndrome after adjusting for age, sex, and requirement of hospital admission (Table III).

Figure 1C summarises the frequency of symptoms reported by patients with post-COVID-19 syndrome and the separated frequencies reported by those who were managed at home and those who required hospital admission.

Discussion

The current evidence on the impact of COVID-19 in patients with systemic autoimmune diseases suggests that these patients have an increased risk of worse outcomes, including a greater risk of hospitalisation/ICU admission and lower survival. Therefore, these patients are considered as a high-risk group for a more complicated COVID-19, especially men, elderly patients, and those with underlying comorbidities (cardiovascular, pulmonary or renal chronic diseases), while other studies have also identified some baseline therapies (corticosteroids, rituximab) and a moderate/high activity at the time of diagnosis of SARS-CoV-2 infection as additional risk factors for a worse evolution of COVID-19 (9). Few specific data are available for individual systemic autoimmune diseases. In pSS, two studies have evaluated the impact

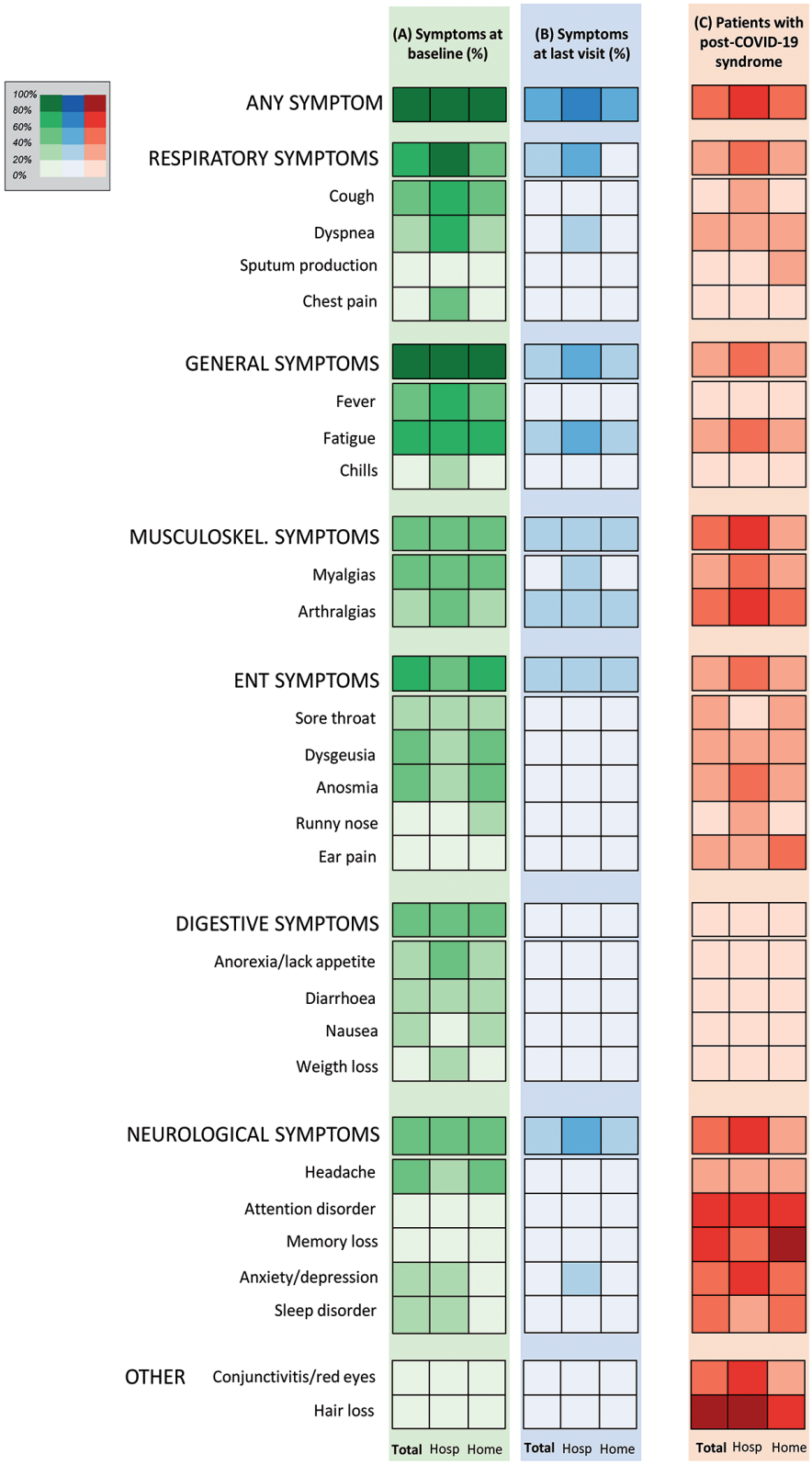

Fig. 1A: Frequency of symptoms related to acute SARS-CoV-2 infection in the entire cohort and the separated frequencies reported by patients managed at home and by those who required hospital admission. **B**: Frequency of symptoms reported by the patients at the last visit in the entire cohort and the separated frequencies reported by patients who were managed at home and by those who required hospital admission.
C: Frequency of symptoms reported by patients with post-COVID-19 syndrome and the separated frequencies reported by those who were managed at home and those who required hospital admission.

of the pandemic in people affected by the disease (13, 14), and only one has described the phenotype of SARS-CoV-2 infection in 51 patients with pSS (15). This study confirmed that the main baseline features associated with a more complicated infection were similar to that identified in non-SS studies, including older age, male sex, chronic comorbidities (pulmonary/kidney diseases), pneumonia (respiratory symptoms and pulmonary infiltrates) and lymphopenia (19).

Until now, there are no studies that have evaluated the persistence of symptoms related to acute SARS-CoV-2 infection in patients with autoimmune diseases, including pSS. This is the first study that has evaluated persistent COVID-19-related symptoms in patients with pSS following acute SARS-CoV-2 infection, and we found that after a mean follow-up of 5 months, 57% remained symptomatic at the last visit of follow-up. Several studies have analysed the frequency of persistent symptoms in people without autoimmune diseases, reporting a wide interval of frequencies ranging from 13% to 70%. The lack of a scientifically accepted definition, together with the limited available evidence and the wide methodological differences among studies, may explain that wide range of reported figures (12). The largest study has evaluated persistence of symptoms in >4,000 people through a mobile application, reporting figures of 13.3% at 4 weeks, 4.5% at 8 weeks and 2.3% at 12 weeks (20). In contrast, two other studies have reported a frequency of persistent symptomatology like that found in our study. Mandal *et al*. (21) evaluated 180 individuals after symptomatic COVID-19 following a similar design to our study and reported that after a mean follow-up of 125 days, 53% had at least one persistent symptom, in particular fatigue, loss of smell and taste, and arthralgia. The second study was carried out in 1655 patients with COVID-19 who required hospitalisation reported that 76% of patients remained symptomatic after 6 months of follow-up, of which 63% were associated with fatigue or muscle weakness (22). Unfortunately, the wide variation in the study design, popula-

Table III. Baseline factors related to the development of post-COVID-19 syndrome in pSS patients.

	Post-COVID-19 syndrome (n=38)	Recovered patients (n=57)	*p*-value	Unadjusted OR [95%CI]	Adjusted OR [95%CI]*
Age, years (mean, range)	54.3 ± 13.3	56.6 ± 14.9	0.443	0.99 [0.96-1.02]	0.97 [0.93-1.00]
Sex, male	2 (5.3)	3 (5.3)	1.000	1.00 [0.13-6.32]	0.60 [0.06-4.50]
Continent, Europe	34 (89.5)	45 (78.9)	0.288	2.27 [0.72-8.67]	2.16 [0.60-9.56]
Comorbidities					
Cardiovascular disease	5 (13.2)	7 (12.3)	1.000	1.08 [0.30-3.68]	0.74 [0.15-3.42]
Pulmonary disease	7 (18.4)	10 (17.5)	1.000	1.06 [0.35-3.06]	0.82 [0.22-2.84]
Smoking (past/active)	7 (18.4)	11 (19.3)	1.000	0.94 [0.32-2.67]	0.96 [0.27-3.17]
Hypertension	11 (28.9)	15 (26.3)	0.963	1.14 [0.45-2.84]	1.48 [0.49-4.48]
Diabetes Mellitus	4 (10.5)	3 (5.3)	0.575	2.12 [0.44-11.31]	1.48 [0.24-9.77]
Obesity	6 (15.8)	5 (8.8)	0.472	1.95 [0.54-7.27]	2.13 [0.52-9.00]
Cancer history	2 (5.3)	4 (7.0)	1.000	0.74 [0.10-3.98]	0.25 [0.03-1.74]
Renal failure	0 (0)	0 (0)	1.000	-	-
COVID diagnosis confirmation			0.481		
PCR+	27 (71.1)	46 (80.7)		REF	REF
Serology+	3 (7.9)	2 (3.5)		2.56 [0.4-20.34]	4.25 [0.62-36.59]
Not tested	8 (21.1)	9 (15.8)		1.51 [0.51-4.43]	1.72 [0.52-5.72]
Fever (≥ 38ºC)	15/28 (53.6)	22/35 (62.9)	0.627	0.68 [0.25-1.87]	0.57 [0.16-1.90]
Respiratory rate (≥ 20BPM)	10/17 (58.8)	10/23 (43.5)	0.522	1.86 [0.53-6.84]	0.59 [0.06-3.93]
Baseline O2 saturation (%)					
≤95%	12/27 (44.4)	7/32 (21.9)	0.117	2.86 [0.94-9.24]	1.63 [0.44-6.03]
≤90%	6/27 (22.2)	2/32 (6.2)	0.160	4.29 [0.89-31.25]	1.59 [0.23-14.43]
Radiological features, pulmonary infiltrate	18/23 (78.3)	15/28 (53.6)	0.123	3.12 [0.94-11.62]	2.68 [0.54-15.30]
Laboratory parameters					
Anaemia	4/24 (16.7)	3/23 (13)	1.000	1.33 [0.26-7.50]	0.55 [0.06-4.91]
Thrombocytopenia	2/24 (8.3)	1/23 (4.3)	1.000	2.00 [0.18-44.9]	3.52 [0.22-100.91]
Leukopenia	2/24 (8.3)	2/23 (8.7)	1.000	0.95 [0.11-8.55]	1.78 [0.17-19.83]
Lymphopenia	15/23 (65.2)	10/23 (43.5)	0.236	2.44 [0.75-8.31]	1.52 [0.36-6.41]
Raised D Dimer levels	12/19 (63.2)	9/16 (56.2)	0.945	1.33 [0.34-5.30]	0.49 [0.02-4.92]
Raised LDH levels	15/21 (71.4)	5/16 (31.2)	0.036	5.50 [1.40-24.74]	6.10 [0.92-53.33]
Raised ferritin levels	6/14 (42.9)	3/11 (27.3)	0.699	2.00 [0.38-12.26]	2.58 [0.28-35.26]
Raised liver enzymes levels	6/24 (25.0)	2/19 (10.5)	0.414	2.83 [0.56-21.20]	2.09 [0.30-19.38]
Raised CRP levels	20/22 (90.9)	14/23 (60.9)	0.046	6.43 [1.40-46.61]	8.60 [1.33-104.44]
COVID-19 treatment					
Hydroxychloroquine	25 (65.8)	20 (35.1)	0.006	3.56 [1.53-8.64]	2.52 [1.00-6.47]
Azithromycin	9 (23.7)	10 (17.5)	0.637	1.46 [0.52-4.04]	0.91 [0.26-2.90]
Oral prednisone	9 (23.7)	13 (22.8)	1.000	1.05 [0.39-2.76]	0.49 [0.13-1.55]
Intravenous methylprednisolone	3 (7.9)	0 (0)	0.120	-	-
Antiviral agents	14 (36.8)	9 (15.8)	0.036	3.11 [1.20-8.47]	1.97 [0.64-6.12]
Tocilizumab	1 (2.6)	1 (1.8)	1.000	1.51 [0.06-39.07]	0.65 [0.02-19.91]
Management, hospital admission	17 (44.7)	8 (14.0)	0.002	4.96 [1.91-13.87]	-
Hospital discharge days after covid dx (mean ± SD)	5.3 ± 8.8	1.7 ± 5.7	0.031	1.08 [1.01-1.17]	1.01 [0.92-1.11]
Complications during admission					
Supplemental oxygen	11 (28.9)	4 (7.0)	0.010	5.40 [1.67-20.96]	2.41 [0.53-11.75]

REF: reference value. *Logistic multivariate regression models adjusting for age, sex and hospital admission.

tions evaluated (unselected, or specifically studied in a particular speciality or pathology) and symptom identification (self-report, a medical evaluation with or without tests), together with the lack of internationally accepted definitions, has resulted in such a high level of heterogeneity that it makes overall analysis and, even more, meta-analysis, very difficult (12).

We identified neuropsychological (47%), musculoskeletal (40%) and general (34%) features among the most frequent persistent symptoms, rather than others more closely related to the involvement of the respiratory tract by the infection such as ENT (34%) and respiratory (31%) manifestations. By organ, the main long-term manifestations observed in other coronaviruses (SARS, MERS) have very clear pathological parallels with SARS-CoV-2, with respiratory, musculoskeletal and neuropsychiatric features being the most frequent persistent features (23, 24). Structuring this wide variety of symptoms and alterations that some COVID-19 patients may present after recovery from acute infection into syndromes that can reasonably group them medically for a better management and identification is challenging. Some studies have suggested differentiated syndromes relating to some symptoms or groups of prominent symptoms, such as general symptoms around fatigue,

ENT symptoms, severe post-pneumonia respiratory consequences or mental health (25).

Information on factors that may identify people at high risk of developing long COVID-19 is still limited. Until now, several studies in non-autoimmune populations have identified as key prognostic factors a specific epidemiological profile: females, older patients, Black, Asian and minority ethnicities (22, 26, 27), some pre-existing conditions (asthma and other respiratory diseases, higher body mass index), dyspnoea at 4–8 weeks follow-up (20), the number of symptoms developed during the acute infection (people with ≥5 symptoms more often had long-term symptoms) (20), and hospitalisation requirement (20). Unfortunately, no information is available for predicting long COVID-19 in patients with autoimmune diseases. This is the first study carried out in patients with autoimmune diseases. We found that those patients with pSS who required hospitalisation were at increased risk of developing the post-COVID-19 syndrome. Although the impact of this syndrome on quality of life is undeniably multidimensional, it appears to be mainly related to the care received according to severity. One study showed that in patients who required ICU admission, the worsened quality of life focused especially on pain and mobility. In contrast, in non-hospitalised patients, it focused on anxiety or depression (28). The severity of illness during acute COVID-19 has also been associated with persistence of symptoms, reduction in health-related quality of life scores, and pulmonary abnormalities caused by the acute viral infection (10).

We found two baseline factors that were associated with the development of post-COVID-19 syndrome independently of hospital admission. The first was the presence of raised CRP levels at the time of diagnosis of SARS-CoV-2 infection, suggesting that a high degree of inflammation in the acute phase of infection could be related to a higher risk of developing persistent symptoms during the follow-up. Although several studies have reported a clear correlation between higher baseline CRP levels and poor outcomes of COVID-19 (29, 30), no study until now has identified this parameter as a predictive factor of developing persistent symptoms. The second factor associated with a high risk of developing post-COVID-19 syndrome was the use of antimalarials. During the first pandemic wave, antimalarials (first chloroquine, then hydroxychloroquine) were considered key therapies against the infection, together with azithromycin and antivirals (lopinavir/ritonavir) (31). The results of controlled trials (RECOVERY and SOLIDARITY) have demonstrated a lack of benefit of using hydroxychloroquine, even reporting an increased mortality (32) and increased cardiac safety risks when combined with azithromycin, especially the vulnerable population (33). In fact, we found that patients who developed post-COVID-19 syndrome were also treated more frequently with azithromycin and antiviral agents, a fact that could be related to the increased rate of hospital admission reported in these patients.

This study has a retrospective, observational design, and therefore, the methodological limitations inherent to this design should be well acknowledged and explained. First, a selection bias cannot be discarded in our study, considering that not all the centres of the SS Big Data Consortium were able to participate in the study. In addition, the great heterogeneity in the accessibility to evaluate the status of infection of all patients with SS among the participating centres (including both symptomatic and asymptomatic cases), that may be different even among regions of the same country, can be an additional bias that may limit the generalisability of our findings. With respect to the aetiology of some symptoms included in the phenotype of post-COVID-19 syndrome that are highly overlapped with SS (fatigue, arthralgias), we cannot exclude that, in some patients, these symptoms could be exacerbated by SARS-CoV-2 infection in patients with a previous history of fatigue/arthralgias and, therefore, they cannot be considered as triggered "de novo" by the virus. In fact, the baseline high frequency of use of hydroxychloroquine (>40%) in our SS patients suggest that a significant percentage could have a previous history of fatigue/arthralgias, which are the symptoms more closely related to prescribing hydroxychloroquine in SS patients. We also found a higher frequency of use of hydroxychloroquine at the time of COVID-19 diagnosis in patients who developed post-COVID-19 syndrome in comparison with those who recovered (in 92% of cases, patients were under this treatment before infection, and hydroxychloroquine was not withdraw at the time of being diagnosed with COVID-19), and a possible explanation is that most of these patients had a previous history of fatigue/arthralgias and, therefore, can be considered a "higher-risk" population for developing a post-COVID-19 syndrome. Finally, our study was not designed to collect specific side effects related to the medications received for SARS-CoV-2 infection, and we cannot stablish a solid link between pharmacological side effects and the development of persistent symptoms.

Little is known about the etiopathogenic mechanisms linked to the symptom persistence in COVID-19. Since long-term manifestations affect various organs and systems, it may have very diverse aetiopathogenic origins, probably driven by an individual genetic predisposition, virus-specific pathophysiologic changes, immune-related damage in response to the acute infection, sequelae of post-critical illness pathological mechanisms of the virus, the phenotypic presentation of the disease in acute infections, and the individual immune response (10). Studies detecting viral RNA persistence in respiratory and extra-respiratory tissues weeks after acute infection are increasingly common, although a clear pathogenic link between viral detection and virus-related organ-specific damage remains unclear (34-38).

In summary, long-term manifestations are increasingly recognised in COVID-19 patients, with systemic clinical presentations affecting a wide range of organs and systems. However, the frequency and natural history of long COVID-19 in patients with systemic autoimmune diseases remain unknown. This is the first study carried out in pa-

tients affected by a systemic autoimmune disease. We found that 57% of patients with pSS affected by COVID-19 remained symptomatic after a mean follow-up of 5 months (more than 40% reported the persistence of four symptoms or more), mainly presenting with anxiety/depression (59%), arthralgias (56%), sleep disorder (44%), fatigue (40%), anosmia (34%) and myalgias (32%). Age-sex adjusted multivariate analysis identified raised levels of serum LDH and CRP levels, use of hydroxychloroquine and antiviral agents, hospital admission, the requirement of supplemental oxygen and duration of hospitalisation as factors associated with a higher risk of developing the post-COVID-19 syndrome. After including hospital admission in the adjusted model, raised CRP levels and the use of hydroxychloroquine remained independent factors. At the population level, it is critical to quantify the burden of long COVID-19 in patients with systemic autoimmune diseases to assess its impact on the healthcare system and appropriately distribute resources, considering the high number of patients that could become long COVID-19 haulers.

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Competing interests

R. Seror reports consulting fees from GSK, Boehringer, Novartis, Janssen, AbbVie, and support for attending meetings from GSK and Amgem. She has been investigator in clinical trials with GSK, Servier, USB, Novartis, Medimmune. The other authors have declared no competing interests.

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