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COVID-19 in systemic lupus erythematosus: Data from a survey on 417 patients

Giuseppe A. Ramirez[a,b,*], Maria Gerosa[c,d], Lorenzo Beretta[e], Chiara Bellocchi[e,f], Lorenza M. Argolini[c,d], Luca Moroni[a,b], Emanuel Della Torre[a,b], Carolina Artusi[c,d], Selene Nicolosi[e], Roberto Caporali[c,d], Enrica P. Bozzolo[b,#], Lorenzo Dagna[a,b,#], On behalf of SMILE, Milan Lupus Consortium

[a] *Università Vita-Salute San Raffaele, Milan, Italy*
[b] *Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy*
[c] *Department of Clinical Science of Community Health and Research Center for Adult and Pediatric Rheumatic Diseases, Università degli Studi di Milano, Milan, Italy*
[d] *Unit of Clinical Rheumatology, ASST Gaetano Pini -CTO, Milan, Italy*
[e] *Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca' Granda Policlinico, Milan, Italy*
[f] *Università degli Studi di Milano, Milan, Italy*

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a chronic disease characterised by autoimmunity and increased susceptibility to infections. COVID-19 is a systemic viral disease currently spreading as a pandemic. Little is known about the impact of COVID-19 in patients with SLE.
Objective: to acquire information on the impact of COVID-19 in SLE.
Methods: A 26-item anonymous questionnaire investigating demographics, SLE clinical features, COVID-19 diagnoses and changes in treatments and daily habits was administered to patients with SLE from three referral centres through www.surveymonkey.com over 10 days. Data from the survey were compared to those from published estimates about the general population.
Results: Four-hundred-seventeen patients responded to the survey. More than 60% of subjects complained of symptoms that are also associated to COVID-19. Fourteen COVID-19 diagnoses (five confirmed by polymerase chain reaction) were reported, in contrast to a 0.73% prevalence of confirmed cases in Lombardy. One hospitalisation was reported. Fever, anosmia, dry cough, a self-reported history of neuropsychiatric SLE and a recent contact with confirmed COVID-19 cases were more strongly associated with COVID-19, as were symptoms and lower compliance to behavioural preventive measures in patients' contacts. No protective effect was seen in subjects on hydroxychloroquine.
Conclusion: COVID-19 morbidity might only moderately be increased in most patients with SLE, although limited information can be inferred on more severe cases. Hydroxychloroquine apparently seems not to confer protection to infection *per se*, although other beneficial roles cannot be excluded. Containment policies and behavioural preventive measures could have a major role in limiting the impact of COVID-19 in patients with SLE.

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Introduction

COVID-19 is a systemic infectious disease with prominent involvement of the respiratory tract, due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. COVID-19 is currently spreading worldwide with a dramatic impact on public health. Italy and specifically the Lombardy region were amongst the first areas hit by COVID-19 pandemic after China. Since February 2020, more than 73,000 reverse-transcriptase polymerase chain reaction (RT-PCR)-proven cases of COVID-19 have been recorded in Lombardy over a

Abbreviations: COVID-19, coronavirus-related disease; cCOVID-19, COVID-19 confirmed by RT-PCR; pCOVID-19, presumptive COVID-19; totCOVID-19, confirmed + presumptive COVID-19; HCQ, hydroxychloroquine; noCOVID-19, patients without COVID-19; NPSLE, neuropsychiatric SLE; RT-PCR, reverse-transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SLE, systemic lupus erythematosus

* Corresponding author at: Università Vita-Salute San Raffaele and Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Via Olgettina 60, 20134, Milan, Italy.
E-mail address: ramirez.giuseppealvise@hsr.it (G.A. Ramirez).
Dr Bozzolo and Prof. Dagna share senior co-authorship

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population of ten million inhabitants, with more than 13,000 deaths [3–5]. These figures probably underestimate the true extent of the pandemic, as the demand for screening tests in the early phase of the contagion overwhelmed the capacity of local laboratories and only subjects with more severe symptoms were actually tested [6, 7]. Estimates based on mortality rates predict a 13% period prevalence of COVID-19 in Lombardy and 0.5–13% (average 4%) in the Italian general population [8, 9]. In vitro data suggest that antimalarials, including hydroxychloroquine (HCQ) might dampen SARS-CoV-2 virulence, by reducing endosomal pH and possibly affecting the post-transcriptional editing of angiotensin converting enzyme 2, the virus receptor on target cells [10, 11], but current in vivo evidence is controversial [12, 13] and randomised-controlled trials are ongoing. International and local guidelines indicate that immunocompromised patients might have a higher risk of infection and of a complicated disease course due to limited capacity to effectively mount an immune response and clear the virus [14, 15]. Patients with systemic lupus erythematosus (SLE) fall in this category, possibly due to drug- and disease-related alterations in the immune response [16].

Systemic lupus erythematosus is a chronic multi-organ autoimmune disease characterised by dysregulated innate and adaptive immune response [17–21]. Antiviral-like interferon-driven mechanisms are thought to have a role in the pathogenesis of SLE [22–24] and viral infections might affect the disease course [25–27]. Antimalarials are pivotal drugs in the treatment of SLE, since they modulate antigen internalisation and processing by phagocytes besides antimicrobial and cardioprotective effects [28–33]. However, accumulation of these drugs into the body over the course of weeks is required before observing any clinically relevant effect [29]. Based on this evidence, it has been hypothesised that a prophylactic effect of HCQ against SARS-CoV-2 might better be evident in patients with SLE who take it routinely (although usually at lower doses), than in the acute phase of COVID-19 [34]. Data regarding the impact of COVID-19 pandemic in patients with SLE are, however, scarce [35, 36]. In order to address this issue in a context where routine clinical visits are limited to emergencies, we set up a web-based survey in the population of patients with SLE in charge to three tertiary referral centres for the city of Milan, Lombardy, Italy.

Methods

Questionnaire

An anonymous 26-item questionnaire (**Supplementary Material 1**) was designed to acquire information on demographics, general clinical features, changes in daily habits and treatments during 12 weeks (February to April 2020). Information regarding family members/cohabitants was also acquired. The number and length of questions and pre-defined answer choices were balanced to maximise information retrieval and minimise time consumption for the responders. We also used a simple language that fitted to a wide lay audience. Face validity was assessed by preliminarily administering the questionnaire draft to five patients. Content validity was assessed by three expert Rheumatologists (MG, LB and EPB), who were also involved in the care of patients with COVID-19, and by a specialist in Infectious Diseases. The questionnaire was hosted from 17th to 27th April 2020 on the SurveyMonkey website (https://it.surveymonkey.com) and patients with SLE under the care of IRCCS Ospedale San Raffaele, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico and ASST Pini-CTO (all members of SMILE, Milan Lupus Consortium) were invited to contribute. The questionnaire and data collection strategy were set up in order to avoid patient-identifiable data collection. Specifically, questions and answers were designed in compliance with the indications of the European Commission for anonymisation [37]. In addition, data acquisition rules through SurveyMonkey were set up in order to disable Internet Protocol address recording.

A preliminary confirmation on the feasibility and compliance of our research strategy and investigational tools with National and International regulations on data protection was acquired from the Ethics Committee and Data Protection Officer of IRCCS Ospedale San Raffaele, Milan, Italy. A specific confirmation that this study did not need additional ethical review was also acquired.

The frequency of demographics and general clinical features amongst responders to the survey were compared to a representative sample [38] of randomly selected patients, who were previously enrolled in the Pan-immuno research protocol, conforming to the Declaration of Helsinki and approved by the Ethics Committee of IRCCS San Raffaele Hospital, Milan, Italy (registry number 22/INT/2018).

Population data

Data regarding the general population in Italy and Lombardy were retrieved from publicly available databases: basic demographics and prevalence of non-COVID-19 diseases were taken from the Italian National Institute for Statistics (ISTAT) [3]; epidemiological data about COVID-19 in the general population from the Italian National Emergency Agency (Protezione Civile) [4], the Italian National Institute of Health (Istituto Superiore di Sanità) [39] and the Regional Government of Lombardy [5].

Statistical analysis

Data were retrieved from SurveyMonkey as digital files formatted for Microsoft Excel®. Microsoft Excel® 2019 and Statacorp STATA® 15 were employed to perform data elaboration and statistical analysis. Categorical variables were compared through the chi-squared test with Fisher's exact correction. Mann-Whitney's U test and Kruskal-Wallis' test were used to compare quantitative variables amongst two or more groups. Given the relatively low number of subjects reporting a diagnosis of COVID-19, significant variables passing a false discovery rate test with a threshold at 0.05 are only reported in order to minimise type I errors.

Results

General clinical features and drug retention rates

Out of 545 invited subjects, 417 (77%) responded to the survey (Table 1) and reported demographics and clinical features substantially consistent with those of 79 randomly selected patients (**Supplementary Table 1**), except for a slightly higher prevalence of fever, thrombocytopenia and weight loss and lower of leukopenia in the survey cohort. Hypertension (30% vs 18%) and allergic disorders (39% vs 12%) were more frequent in responders than what expected in the general population ($p<0.001$ for both variables). Seventy-one percent of the responders reported that the epidemic had affected their daily routine (Fig. 1**A**). More than 60% of the participants reported at least one symptom included in the COVID-19 clinical spectrum, the most frequent being myalgia (31%), rhinorrhoea (25%), fever (17%) and dry cough (16%). The prevalence of COVID-19-related symptoms was lower amongst responders' family members/cohabitants, (Fig. 1**B**). The majority of participants to the survey adopted multiple measures to cope with the risk of SARS-CoV-2 infection. However, adherence to the same measures by their family members/cohabitants was reported to be significantly lower (**Supplementary Figure 1**).

Of 417 responders, 389 (93%) reported to be on one or more drugs for SLE with 289 being on HCQ alone (39%) or in combination with immunosuppressants. Forty responders (10%) reported to have reduced or discontinued at least part of their medication. The most

Table 1
reported demographics and clinical features in comparison with the general population

	Responders to the survey	General population (Italy) [3]§	General population (Lombardy region) [3]§
Number of subjects	417	60,359,546	10,060,574
Females: n (%)	379 (91)	30,974,780 (51)	5,136,123 (51)
Males: n (%)	38 (9)	29,384,766 (49)	4,924,451 (49)
Subjects living in Lombardy: n (%)		10,060,574 (17)	10,060,574 (100)
Age groups (years)	332 (80)		
18–25	16 (4)	4,786,752 (8)	761,884 (8)
26–30	33 (8)	3,265,501 (5)	520,738 (5)
31–35	38 (9)	3,405,361 (6)	567,808 (5)
36–40	48 (11)	3,815,848 (6)	649,145 (6)
41–45	54 (13)	4,551,276 (8)	785,596 (8)
46–50	50 (12)	4,852,030 (8)	834,472 (8)
>50	178 (43)	26,003,644 (43)	4,285,859 (43)
Comorbidities: n (%)			
None	80 (19)	15,874,560 (26)^	2,173,084 (22) ^
Arterial hypertension	124 (30)	10,925,081 (18)^	1,750,540 (17) ^
Myocardial infarction	19 (5)	ND	ND
Chronic heart failure	9 (2)	ND	ND
Stroke	19 (5)	ND	ND
Diabetes	13 (3)	3,380,136 (6)^	462,786 (5) ^
COPD	18 (4)	3,621,574 (6)^	684,119 (7) ^
Malignancy	31 (7)	ND	ND
Haematological malignancy	4 (1)	ND	ND
Asthma	24 (6)	ND	ND
Drug allergy	109 (26) All 163 (39)	7,001,709 (12)^	1,307,875 (13)^
Allergy to food, inhalants (pollens, grasses, dustmites…), insect venom	82 (20)		
Other	120 (29)	ND	ND
SLE duration (years)			
<2	36 (9)	NA	NA
2–10	125 (30)		
>10	256 (61)		
SLE clinical features: n (%)			
None	14 (3)		
Skin inv.	206 (49)		
Joint inv.	275 (66)		
Renal inv.	152 (36)		
Nervous system inv.	78 (19)		
Serositis	107 (26)		
Leukopenia	151 (36)	NA	NA
Thrombocytopenia	118 (28)		
Anaemia	112 (27)		
Fever	210 (50)		
Lymph-node enlargement	141 (34)		
Weight loss	123 (29)		
Fatigue	341 (82)		
Unknown	20 (5)		
COVID-19 confirmed by RT-PCR (cCOVID-19): n (%)	5 (1.20)	199,414(0.33)[+]	73,479 (0.73)[+]
Presumptive COVID-19 (pCOVID-19): n (%)	9 (2.16)	ND	ND
Total COVID-19 (totCOVID-19): n (%)	14 (3.36)	Estimated 2,414,383 (4.0)[~]	Estimated 1,338,056 (13.3)[~]
Hospitalisations due to COVID-19: n(%)	1 (0.24)*	ND	42,889 (0.43)[¨]

§ as of January, 1st 2019 unless otherwise specified | ^Data referring to 2018 | + Data from ref. [4] as of April, 27th 2020 | ~ according to ref. [8] | * in one additional case an admission for potential COVID-19 symptoms did not associate with a diagnosis of COVID-19 | ¨ assuming all deaths having occurred in-hospital (data from [5]) as of April, 27th 2020 | ND: no data | NA: not applicable.

frequent reason for these changes was Physician's indication. Drug shortage was reported in 36% and 17% of responders who reduced or discontinued HCQ or immunosuppressants, respectively. Seventy-five percent of these subjects in both groups attributed this event to issues related to the COVID-19 pandemic (Fig. 1**C**–**J**).

COVID-19 cases and hospitalisations

Five responders (1.2%, four living in Lombardy) reported a RT-PCR-confirmed diagnosis of COVID-19 (cCOVID-19). Nine subjects (2.2%, all residents in Lombardy) reported a presumptive diagnosis COVID-19 based on symptoms or other tests (pCOVID-19; Table 1). The global frequency of COVID-19 (confirmed + presumptive diagnoses, totCOVID-19) was 3.4% (4.2% amongst subjects living in Lombardy). Five subjects were tested for SARS-CoV-2 with negative results. Ten all-cause hospitalisations were reported, yielding a hospitalisation rate of 10 admissions/100 person-years. One hospitalisation involved a subject with COVID-19, thus the frequency of COVID-19 hospitalised patients in our cohort was 0.24%, compared to 0.43% in the general population of Lombardy [5]. Out of ten hospitalised subjects, two eventually became cCOVID-19. Nineteen subjects (5%, four cCOVID-19) reported previous contacts with other confirmed COVID-19 cases. In addition, nine responders reported to have had at least one family member/cohabitant with a diagnosis of COVID-19 (five confirmed by RT-PCR). Three of them (33%) were eventually diagnosed with COVID-19.

Associations with clinical features and treatments

Confirmed cases (cCOVID-19)

Hypertension, anosmia, ageusia and a recent history of exposure to COVID-19 confirmed cases were more frequent amongst cCOVID-

Fig. 1. patients' status during the study timeframe and drug retention rates. In this figure, variations in patients' status and treatments during the 12-week observation timeframe is reported. Panel A depicts the percentage of responders to the survey who reported that current pandemic had affected their routine activity to some extent. Panel B provides a visual summary of the relative frequencies of multiple symptoms potentially attributable to COVID-19 in responders to the survey (light blue) and their relatives (light orange). The former group had a higher prevalence of symptoms. Panel C describes the number and relative frequency of responders who reported taking hydroxychloroquine (HCQ), mofetil mycophenolate (MMF), azathioprine (AZA), cyclosporin A (CSA), belimumab (BEL), methotrexate (MTX), other immunosuppressants or no drug as their standard therapy. Panel D depicts the number and relative frequency of responders who reported taking prednisone at different doses. Panel E and H show the percentage of patients who continued, reduced or discontinued their treatment with HCQ or any immunosuppressant (including prednisone) respectively. Panel F and I describe the reasons reported for HCQ

19 cases than in subjects denying any COVID-19 diagnosis (noCOVID-19, Table 2). In addition, cCOVID-19 cases were associated with dyspnoea ($p = 0.001$), myalgia ($p = 0.003$), rhinorrhoea ($p = 0.030$), anosmia ($p = 0.009$) and ageusia ($p = 0.002$) in their family members/cohabitants.

Presumptive diagnoses (pCOVID-19)

Subjects with pCOVID-19 were more frequently younger than 40 years of age and showed a lower prevalence of hypertension and anosmia than those in the cCOVID-19 group. In addition, none of them was exposed to confirmed COVID-19 cases (Table 2). Responders with pCOVID-19 also differed from noCOVID-19, as they had a higher prevalence of self-reported neuropsychiatric SLE (NPSLE) and of recent fever and dry cough (Table 2). Mycophenolate use was more frequent in pCOVID-19 compared to noCOVID-19 ($p = 0.024$). Family members/cohabitants of subjects with pCOVID-19 were reported to adopt less strict measures of home confinement compared to those related to noCOVID-19 cases ($p = 0.038$).

Aggregate diagnoses (totCOVID-19)

Subjects in the totCOVID-19 group had a higher prevalence of self-reported NPSLE, recent fever, dry cough, anosmia, ageusia and had more frequently a history of exposure to confirmed COVID-19 cases compared to noCOVID-19 (Table 2). Lower rates of smart-working measures ($p = 0.041$) amongst subjects, and higher rates of recent dyspnoea ($p = 0.012$), myalgia ($p = 0.025$) and ageusia ($p = 0.002$) amongst family members/cohabitants were also reported.

Comparisons amongst groups

Multigroup comparisons confirmed that age lower of equal than 40 years, self-reported NPSLE, hypertension history, recent fever, dry cough, anosmia or ageusia, use of mycophenolate, recent treatment discontinuation, exposure to confirmed COVID-19 cases and recent dyspnoea, rhinorrhoea, myalgia, anosmia or ageusia amongst family members/cohabitants were differentially expressed amongst cCOVID-19, pCOVID-19 and noCOVID-19 (all p values <0.05 after false discovery rate). No additional associations were found with clinical or treatment features. In particular, no association was found amongst being on HCQ, prednisone or immunosuppressants other than mycophenolate and COVID-19 (cCOVID-19, pCOVID-19, totCOVID-19) or achievement of these outcomes in subjects who reported exposure to confirmed COVID-19 cases.

Discussion

The reciprocal interaction between dysregulation of the immune response and infections in SLE is complex and only partially understood [25, 40]. Annual influenza pandemics constitute potential triggers for SLE flares and can be prevented by vaccination campaigns, which reduce hospitalisation rates, morbidity and mortality [41]. The current COVID-19 pandemic is unprecedented both for clinical/pathophysiological aspects such as the lack of immunological memory to SARS-CoVs in the general population (in contrast to influenza) and for public health, in the absence of vaccines and clearly effective treatments. This study was designed to acquire information on the impact of COVID-19 in patients with SLE from the first Western Country hit by the pandemic. Our survey covered the 12 weeks from the putative onset of the outbreak in Italy to its peak [4]. The results of this study suggest that during this time, at least 1.2% of patients with SLE had cCOVID-19. An additional nine subjects in our cohort were diagnosed with pCOVID-19 rising this estimation to 3.4%. Although, both figures are higher than current proportion of confirmed cases in the general population of Italy (0.33%) and Lombardy (0.73%), based on confirmed cases [4], which, in addition, suggest an even lower impact of COVID-19 in young women [39]. Therefore, these data might also be consistent with preliminary reports from rheumatological registries [36]. It is however possible that this difference could be biased, since patients with underlying diseases or taking immunosuppressive medications might have been tested more than the general population. Indeed, these percentages fall well within the predicted range of "real" cases based on mathematical models [8, 9]. We found a hospitalisation rate of 10 admissions/100 person-years, in line with previous works [42, 43]. Hospitalisation rates for COVID-19 were also comparable to those reported in Lombardy to date [5], although the latter only consider confirmed cases. Conversely, our data may underestimate the number of more severe cases, who being possibly ill at the time of the administration of our questionnaire might have not been able to fill it. In addition, due the design of our study, we do not have information about the course of the reported admission for COVID-19. The majority of responders to our survey complained of one or more potential COVID-19-associated symptoms, with a prominence of fever, dry cough, anosmia and ageusia in association with a diagnosis of COVID-19 over less specific symptoms such as myalgia, which might have been not pointed out due to the SLE background. The potential association of COVID-19 with self-reported NPSLE deserves a deeper investigation. Interestingly, although fewer symptoms were reported amongst responders' family members/cohabitants than amongst responders themselves, these were strongly associated with COVID-19. Furthermore, the inverse association between family members/cohabitants' compliance to behavioural preventive measures and COVID-19, highlights the importance of containment policies for the safety of patients with chronic illnesses. This consideration is in fact consistent with general preliminary data on patients with rheumatic diseases from the Lombardy region [44, 45]. Amongst SLE-comorbidities we found a high prevalence of hypertension, which was associated with cCOVID-19 as previously reported. Notably, no clear association was found between HCQ and absolute protection from COVID-19, in line with a very recent report [35], although the concomitant use of immunosuppressants in 61% of the responders might have affected these results and masked some potential effects of HCQ in contrasting factors such as dysregulated inflammation with impaired pathogen clearance and enhanced interferon-mediated responses which might potentiate SARS-CoV-2 virulence [16, 46]. Also, it is not possible to exclude that somehow HCQ might have mitigated the course of COVID-19 in these patients: indeed our questionnaire did not address the severity of COVID-19 course, which could have been differentially expressed under distinct treatment regimens.

For this study, we chose to employ a web-based anonymous survey. This approach has multiple limitations. In particular, the information provided by the responders could not be supervised and verified for clinical accuracy. Accordingly, further studies based on direct patient interview and correlation with data in clinical charts are needed to confirm our data. In addition, we could not retrieve information on potentially severe cases of SARS-CoV-2 infection and on COVID-19 mortality, pointing to the need for larger population-based studies, possibly corroborated by laboratory data such as serological studies for SARS-CoV-2 in the study population. Notwithstanding these limitations, we believe that our study provides some important clues to inform patients' management and future studies in this field. To this purpose, the use of a web-based approach to rapidly and homogeneously collect a relatively large amount of data

or immunosuppressant reduction or discontinuation respectively: α by indication from a Physician; β: drug shortage or other logistic issues; γ: personal patient's choice. Panel G and J show the responses to the question whether reduction or discontinuation of HCQ and immunosuppressant (respectively) could be attributed to the COVID-19 pandemic according to the patient's opinion. In these panels, responders are stratified by their response to the reasons for drug changes as in panels F and I.

Table 2
clinical features of responders with COVID-19.

	COVID-19 in responders to the survey			noCOVID-19 (*n* = 376)
	cCOVID-19 (*n* = 5)	pCOVID-19 (*n* = 9)	totCOVID-19 (*n* = 14)	
Females: n (%)	5 (100)	9 (100)	14 (100)	343 (91)
Subjects living in Lombardy: n (%)	4 (80)	9 (100)	13 (93)	303 (81)
Age groups				
18–25	0 (0)	0 (0)	0 (0)	15 (4)
26–30	0 (0)	2 (22)	2 (14)	15 (4)
31–35	0 (0)	2 (22)	2 (14)	15 (4)
36–40	0 (0)	2 (22)	2 (14)	15 (4)
41–45	2 (40)	1 (11)	3 (21)	15 (4)
46–50	2 (40)	1 (11)	3 (21)	46 (12)
>50	1 (20)	1 (11)	2 (14)	160 (43)
Age ≤40 vs >40	0 (0) vs 5 (100)^	6 (67) vs 3 (33)	6 (43) vs 8 (57)	122 (32) vs 254 (68)
Comorbidities				
None	0 (0)	2 (22)	2 (14)	71 (19)
Arterial hypertension	4 (80)*^	1 (11)	5 (36)	113 (30)
Myocardial infarction	0 (0)	0 (0)	0 (0)	18 (5)
Chronic heart failure	0 (0)	1 (11)	1 (7)	8 (2)
Stroke	0 (0)	1 (11)	1 (7)	15 (4)
Diabetes	0 (0)	0 (0)	0 (0)	12 (3)
COPD	0 (0)	0 (0)	0 (0)	16 (4)
Malignancy	0 (0)	0 (0)	0 (0)	30 (8)
Haematological malignancy	0 (0)	0 (0)	0 (0)	4 (1)
Asthma	0 (0)	0 (0)	0 (0)	24 (6)
Drug allergy	3 (60)	1 (11)	4 (29)	98 (26)
Other Allergies	2 (40)	2 (22)	4 (29)	77 (20)
Other	0 (0)	4 (44)	4 (29)	109 (29)
SLE duration (years)				
<2	0 (0)	0 (0)	0 (0)	34 (9)
2–10	1 (20)	5 (56)	6 (43)	113 (30)
>10	4 (80)	4 (44)	8 (57)	229 (61)
SLE clinical features: n (%)				
None of the following	0 (0)	0 (0)	0 (0)	12 (3)
Skin inv.	3 (60)	6 (67)	9 (64)	185 (49)
Joint inv.	4 (80)	6 (67)	10 (71)	246 (65)
Renal inv.	2 (40)	3 (33)	5 (36)	137 (36)
Nervous system inv.	2 (40)	5 (56)§	7 (50)~~	66 (18)
Serositis	3 (60)	4 (44)	7 (50)	92 (24)
Leukopenia	2 (40)	3 (33)	5 (36)	136 (36)
Thrombocytopenia	2 (40)	3 (33)	5 (36)	104 (28)
Anaemia	1 (20)	2 (22)	3 (21)	100 (27)
Fever	5 (100)	4 (44)	9 (64)	187 (50)
Lymph-node enlargement	3 (60)	4 (44)	7 (50)	128 (34)
Weight loss	1 (20)	4 (44)	5 (36)	108 (29)
Fatigue	4 (80)	7 (78)	11 (79)	307 (82)
Unknown	0 (0)	0 (0)	0 (0)	19 (5)
VAS (1–10): median (IQR)	8 (5–9)*	6 (4–9)§	7 (4–8)~~	5 (3–7)
Therapy: n (%)				
Usually on HCQ	3 (60)	8 (89)	11 (79)	259 (69)
Discontinued/reduced HCQ	1 (33)	1 (13)	2 (18)	20 (8)
Usually on PDN	2 (40)	5 (56)	7 (50)	164 (44)
Usually on immsupp.	4 (80)	6 (67)	10 (71)	246 (65)
Discontinued/reduced immsupp. or PDN	2 (40)*	2 (22)	4 (29)	19 (5)
Symptoms: n (%)				
None	0 (0)	3 (33)	3 (21)	139 (37)
Fever	2 (40)	5 (56)§§	7 (50)~~	59 (16)
Dry vs non-dry cough	1 (20) vs 0 (0)	5 (56)§§ vs 0 (0)	6 (43)~ vs 0 (0)	59 (16) vs 53 (14)
Dyspnoea	1 (20)	1 (11)	2 (14)	36 (10)
Myalgia	2 (40)	5 (56)	7 (50)	113 (30)
Rhinorrhoea	3 (60)	1 (11)	4 (29)	95 (25)
Sore throat	1 (20)	2 (22)	3 (21)	69 (18)
Anosmia	3 (60)***^	0 (0)	3 (21)~	14 (4)
Ageusia	2 (40)*	1 (11)	3 (21)~	14 (4)
Conjunctivitis	2 (40)	2 (22)	4 (29)	58 (15)
Diarrhoea	0 (0)	1 (11)	1 (7)	58 (15)
Nausea/loss of appetite	1 (20)	1 (11)	2 (14)	33 (9)
Number of symptoms: median (IQR)	3 (2–6)	3 (0–5)	3 (1–4)~	1 (0–3)
Contact with a COVID-19 case: n (%)	4 (80)***^	0 (0)	4 (29)~~	14 (4)

IQR: Interquartile range.
*, **, ****: $p<0.05$, $p<0.01$ and $p<0.001$ vs noCOVID-19 respectively.
^,^^: $p<0.05$ and $p<0.010$ vs pCOVID-19 respectively.
§, §§: $p<0.05$ and $p<0.010$ vs noCOVID-19 respectively.
~,~~: $p<0.05$ and $p<0.010$ vs noCOVID-19 respectively.

constitutes a promising way to overcome the limitations posed by the pandemic to the usual research practice. In addition, this kind of tool proved advantageous in minimising potential biases due to the Physician's influence or arbitrary filtering on patients' responses and in promoting patients' engagement [47]. We believe that this had a striking role in acquiring "real-life" data on compliance to containment measures and drug use as well as on the whole spectrum of symptoms experienced by the patients during the pandemic, enforcing their potential value for future research.

In conclusion, data from a web-based survey support the hypothesis that COVID-19 real prevalence might be significantly underestimated. Although an only moderate increase in morbidity has been reported from a large number of patients with SLE in our study, compared to the general population, information on potential associations between SLE and more severe COVID-19 cases is still incomplete. The combination of SLE and COVID-19 may express into a large spectrum of clinical phenotypes, due to the large variety of disease- and drug-related detrimental and protective factors potentially coexisting within distinct patients with SLE. New-onset fever, anosmia and dry cough, and recent contacts with confirmed COVID-19 cases or symptomatic family members/cohabitants, might enforce the suspicion of COVID-19 in patients with SLE. In the absence of effective treatments and of a proven effect of HCQ towards COVID-19, the strong association amongst COVID-19 and insufficient protection from surrounding contacts might indicate that strict compliance to behavioural preventive measures should be emphasised in this setting.

Authors' contributions

All authors contributed to the general design of the study and of the questionnaire. GAR analysed the data and drafted the paper. All authors contributed to the critical analysis of the results and to revise the manuscript draft. All authors approved the final version of the article and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work will appropriately be investigated and resolved.

Declaration of Competing Interest

The authors declare no conflict of interest in connection with this paper

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.semarthrit.2020.06.012.

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