Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Full Length Article

Impact of the COVID-19 pandemic in patients with systemic lupus erythematosus throughout one year

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ABSTRACT

Little is known about the impact of coronavirus disease 2019 (COVID-19) pandemic to the care of patients with systemic lupus erythematosus (SLE) in the long-term. By crossing population data with the results of a web-based survey focused on the timeframes January–April and May–December 2020, we found that among 334/518 responders, 28 had COVID-19 in 2020. Seventeen cases occurred in May–December, in parallel with trends in the general population and loosening of containment policy strength. Age > 40 years ($p = 0.026$), prednisone escalation ($p = 0.008$) and infected relatives ($p < 0.001$) were most significantly associated with COVID-19. Weaker associations were found with asthma, lymphadenopathy and azathioprine or cyclosporine treatment. Only 31% of patients with infected relatives developed COVID-19. Healthcare service disruptions were not associated with rising hospitalisations. Vaccination prospects were generally welcomed. Our data suggest that COVID-19 has a moderate impact on patients with SLE, which might be significantly modulated by public health policies, including vaccination.

1. Introduction

Cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related disease (COVID-19) are accumulating around the world with dramatic consequences in terms of life expectancy, biological and psychological morbidity as well as social and economic stability [1–3]. Public health policies, including containment measures and, more recently, vaccination campaigns have become crucial to contrast the effects of the pandemic [4]. In parallel, an unprecedented international effort has led to significant advancement in understanding COVID-19 pathophysiology. In this context, the differential performance of interferon (IFN)-driven and antibody-mediated immune responses among individuals emerged as a pivotal mechanism in determining the clinical course of the disease [5]. Curiously, this landmark discovery disclosed an unexpected pathophysiological similarity between acute COVID-19-related inflammatory events and chronic aberration in the deployment of the immune response as observed in patients with systemic lupus erythematosus (SLE) [6–8]. Moreover, evidence of a potential association between SLE-related pre-pandemic anti-IFN antibodies and COVID-19 has been provided by some authors [9]. These data further stimulated

Abbreviations: ACE, angiotensin converting enzyme; COVID-19, SARS-CoV-2-related disease; cCOVID, COVID-19 cases confirmed by reverse transcriptase polymerase chain reaction; IFN, interferon; IQR, interquartile range; noCOVID, patients who were not diagnosed with COVID-19; NRS, numerical rating scale; pCOVID, presumed COVID-19 cases, based on symptoms, serological or imaging findings; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SLE, systemic lupus erythematosus; totCOVID, cCOVID + pCOVID cases.

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a general interest in studying the impact of SARS-CoV-2 infection in patients with SLE, who bear a unique combination of potential protective and detrimental factors for COVID-19 and might also constitute a paradigm to assess the wider social impact of the pandemic in persons with chronic diseases [3,10–12]. In fact, while favourable demographics (SLE is more frequent in young women, who have lower risk of severe COVID-19), hyperactive antiviral-like IFN-responses and potential prevention of COVID-related cytokine storm manifestations by chronic immunosuppression/immunomodulation could have constituted potential protective factors for patients with SLE, dysregulation of IFN responses together with altered epigenetics of angiotensin converting enzyme 2 (ACE2, the human target of SARS-CoV-2) and impairment of physiological immune responses by immunodepression might have behaved in the opposite way [9,13–15].

At a clinical level, a slightly increased COVID-19 morbidity has been reported in patients with SLE and other rheumatic diseases in comparison to the general population [11,12,16]. Nonetheless, a significant geographical variability is consistently detectable among different studies [17–19], possibly suggesting that local factors including population-level containment strategies [10,11,20,21] might affect the global impact of COVID-19 pandemic on patients with SLE. In addition, experimental strategies also varied among studies. Multi-national registries focused on clinical features and disease course of patients with rheumatic diseases and COVID-19 and continuously provide data of increasing robustness about potential risk factors for severe or fatal outcomes, beside potential limitations due to the lack of non-COVID control groups and risk of overreporting of more severe cases [22–24]. Other researchers analysed population-based data and public health databases, thus complementing registry information with a bird's-eye view of contagion dynamics in patients with rheumatic diseases in the frame of the general population [18,19,25]. Complementary to these approaches, cohort studies based on questionnaires or chart review were also frequently reported [3,10,26–30] and provided a deeper insight into the multifaceted clinical, social and psychological impact of the pandemic in the specific settings of patients with selected rheumatic diseases or general inflammatory disorder cohorts, despite potential limitations in capturing more severe cases [11,12].

Similar to other Countries in Europe and around the world, Italy was severely hit by the pandemic, with a first surge of cases in February–April 2020 and a second peak in November 2020 [31]. Of note, public health measures implemented during these two timeframes differed significantly, with looser rules prescribed during the second contagion wave when a three-colour regional risk classification was applied (high-risk = “red”, intermediate-risk = “orange”, and low-risk = “yellow”) as compared to a homogenous country-wide “red”-zone instituted during the first wave [32]. While data about the early impact of COVID-19 in patients with SLE are accumulating, little is known about the global effects of the pandemic in the medium/long-term, also in light of emerging topics, such as the ongoing vaccination campaigns. To address this issue, we performed a web-based survey in a multicentre cohort of patients with SLE referring to three tertiary care hospitals in the Milan metropolitan area.

2. Methods

2.1. Questionnaire

From January 4th to 14th 2021, 518 patients routinely followed up at IRCCS Ospedale San Raffaele, ASST Pini-CTO and Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico (all members of SMILE, Milan Lupus Consortium) were invited to take a web-based anonymous [33] survey (Supplementary Material) hosted on the surveymonkey.com platform and covering the clinical events of the entire year 2020. Patients were instructed to avoid multiple registrations. Face and content validity of the questionnaire were assessed by direct interview of five randomly selected patients and by consensus among three expert rheumatologists (LB, EPB, MG) and a specialist in Infectious diseases, respectively. The questionnaire encompassed general demographics and clinical features, exposure to subjects with definite COVID-19 and occurrence of COVID-19 in patients. Numerical rating scales (NRS) ranging from zero (no compliance) to ten (strict compliance) were included to assess patients' and patients' family members' attitudes towards behavioural measures across the two pandemic waves. As data from the first pandemic wave have already been reported, we focused some additional questions, including prevalence of potential COVID-19 symptoms, hospitalisations and cases of COVID-19 among patients' family members/cohabitants, on the second observation period only. Data were also acquired about patients' attitude towards COVID-19 vaccination and about their perception of the impact of the pandemic on SLE course and management. The questionnaire was built in compliance with the European Guidelines for anonymisation [33] and after confirmation by the Ethics Committee and Data Protection Officer of IRCCS Ospedale San Raffaele, Milan, Italy that no further approval was required for this study.

2.2. Definitions of COVID-19 cases and timeframes

We defined cases diagnosed through reverse-transcriptase polymerase chain reaction as confirmed cases (cCOVID). Cases of COVID-19 diagnosed by a Physician on the basis of clinical features, radiological findings or a positive serology were labelled as presumptive cases (pCOVID). Total cases with COVID-19 (totCOVID) identified patients with either cCOVID or pCOVID in contrast to patients without COVID-19 (noCOVID) [21,34]. We identified two timeframes of interest: January to April 2020 (first period) and May to December 2020 (second period), based on trends of infection curves in Italy [35].

2.3. Validation

In order to test the consistency of responders' features with the general demographics and clinical features of the reference cohort, we analysed a representative [36] random sample of 75 patients routinely followed up in one of our three reference centres. Furthermore, to validate the reliability of our dichotomic observation timeframe for epidemiological analyses, we screened all visits performed from January to May 2021 for COVID-19 cases having occurred in 2020. New patients were excluded. This section of the study involved patients enrolled upon informed consent in a larger observational protocol (Pan-immuno), approved by the Institutional Review Board of IRCCS San Raffaele Hospital, Milan, Italy under registry number 22/INT/2018.

2.4. Population data

General demographic, epidemiological, and public security data were retrieved from publicly accessible databases under the Italian National Institute of Statistics [37], National Emergency Agency (Protezione Civile) [35], National Institute of Health (Istituto Superiore di Sanità) [31] and Ministry of Internal Affairs [38] and from the Official Gazette of the Italian Republic (https://www.gazzettaufficiale.it/).

2.5. Statistical analysis

The chi-squared test with Fisher's exact correction was used to compare the relative frequency of categorical variables among groups. The Mann-Whitney's *U* test or the Student's *t*-test were used to assess differences in quantitative variables among two groups under non-normally or normally distribution settings, respectively. Kruskal-Wallis' or ANOVA tests were employed in the same way for comparisons involving more than two groups. Microsoft Excel® 2019 and Statacorp STATA® version 15.0 were used for data elaboration and statistical analysis. Data are expressed as median (interquartile range, IQR) unless otherwise specified.

3. Results

3.1. Demographics, general clinical and treatment features

A total of 334 patients (out of 518 invited, 64%), responded to the survey. Two-hundred-seventy-one (81%) participated to a previous survey addressing the impact of COVID-19 during the first pandemic wave [21]. Most patients were women (301/334, 90%), older than 40 years of age (209/334, 63%) with disease duration exceeding 10 years (205/334, 61%). Joint and skin involvement along with fatigue were the most frequent SLE features, while hypertension and allergy represented the most frequent comorbidities (Table 1). Demographics and general clinical features were consistent with those of a representative random sample of patients from the same cohort and with data from the previous survey [21], except for slightly different frequencies of joint involvement and constitutional symptoms (Supplementary Table 1). Patient self-reported global health status on a 0–10 NRS (with 10 representing the optimal status) was 7 (6–8) at time of taking the survey. The majority of patients reported being on hydroxychloroquine (235/334, 70%); 211/334 (63%) were on one or more immunosuppressants; 233/334 were on prednisone and 128 of them (55%) were taking less than 5 mg/day prednisone equivalents. Ninety-seven patients (29%) reported treatment escalation at least once during the course of 2020. Sixty patients (62%) required increased prednisone dose, 49 (51%) new or potentiated immunosuppressants, 23 (7%) addition of belimumab. Conversely, 114 patients (34%) reported that during 2020 their disease was enough controlled to allow tapering of prednisone (78/114, 68%) and/or immunosuppressants (40/114, 35%); in three cases belimumab could also be withdrawn (Table 1). Two-hundred-twenty-eight patients (68%) reported having missed one or more scheduled appointments due to healthcare service disruption secondary to the pandemic. For 179/329 responders (54%) the pandemic had no significant impact on the course of their disease; 56 (17%) reported a worsening impact; 12 (4%) felt that the pandemic had somehow been beneficial for their disease; 82 (25%) were uncertain about how the pandemic had possibly affected the course of SLE.

3.2. COVID-19 cases in 2020

Twenty-eight patients (8%) reported a diagnosis of COVID-19 during 2020. Eleven totCOVID cases (three cCOVID, eight pCOVID) reportedly occurred before May 2020 (first period), and 16 (15 cCOVID, one pCOVID) from May to December 2020 (second period). One patient reported to have repeatedly been classified as cCOVID both in the first and second period. The total annual incidence of cCOVID among responders to the survey was 19/334 (6%). Consistently, among 217 patients seen during routine outpatients visits from January to May 2021, 15 (7%) had a history of cCOVID ($n = 12$) or pCOVID ($n = 3$) during 2020: five cases occurred between February and April 2020, one in September and nine in November 2020. Compared to survey responders with noCOVID, responders with totCOVID were more frequently older than 40 years of age (23/28 vs 186/306; $p = 0.026$), had more frequently a history of SLE-related lymphadenopathy (17/28 vs 121/306; $p = 0.043$) and of asthma (5/28 vs 17/306, $p = 0.028$). Patients who needed treatment escalation throughout 2020 (13/28 vs 84/306; $p = 0.048$), especially with prednisone (11/28 vs 49/306; $p = 0.008$) were more frequent in the totCOVID than in the noCOVID subgroup. Therapy with prednisone (24/28 vs 209/306; $p = 0.056$), azathioprine (8/28 vs 37/306; $p = 0.037$) and cyclosporine A (5/28 vs 7/306; $p = 0.002$) were also relatively more frequent in patients with totCOVID than in patients with noCOVID (Table 1).

3.3. Comparisons among the two phases

During the two observation timeframes a total of 204,335 and 1,905,198 cases of COVID-19 were respectively recorded in Italy, yielding a crude annual incidence rate of 4%. To contrast the spread of the contagion, multiple activities were banned or subject to limitations, with looser rules in the second period. Individual or business compliance to behavioural rules was checked regularly. However, the median number of checks/month to persons and businesses in the second observation period was significantly lower than in the first period [2.08 (1.82–2.36) x 10^6 vs 5.83 (3.88–7.77) x 10^6, $p = 0.068$ for individuals; 0.36 (0.25–0.47) x10^6 vs 2.27 (1.75–2.80) x10^6, $p = 0.037$ for businesses; Fig. 1).

Regarding patients taking the survey and their families, there were no differences in self-reported compliance to the use of gloves or masks between the first and the second period. Patients' compliance to the prescription to adopt smart-working measures did also not change among the two observation timeframes, in contrast to patients' family members/cohabitants, who almost invariably returned to their usual work practices [compliance NRS = 0 (0–8) in the second period vs 3 (0−10) in the first period; $p = 0.032$]. Both patients and patients' family members/cohabitants showed lower compliance to lockdown measures in the second period than in the first period [compliance NRS = 7 (5–9) vs 8 (5–10); $p < 0.001$ for patients; 7 (3–9) vs 8 (5–10); $p < 0.001$ for patients' family members/cohabitants]. Exposure to confirmed COVID-19 cases was reported by 23 patients in the first period, 63 patients in the second period and 22 in both periods. Nineteen of these 108 patients with at least one contact with COVID-19 (18%) eventually had COVID-19, in contrast to 9/226 totCOVID cases among patients with no contact with other confirmed cases of COVID-19 ($p < 0.001$).

3.4. Specific features of the second observation timeframe

During the second observation period, 36 patients reported to have had at least one family member/cohabitant with COVID-19. Of these, only 11 (31%) were eventually classified as totCOVID (compared to 6/288, 2% totCOVID among patients with no family/member cohabitants with COVID-19; $p < 0.001$). Compared to the other 25 patients with potential family contacts with COVID-19, these 11 patients were more frequently older than 40 years (10/11 vs 11/25; $p = 0.011$) and tended to be more frequently on immunosuppression (10/11 vs 16/25; $p = 0.127$), while no difference was observed in terms of immunomodulation with hydroxychloroquine (8/11 vs 18/25) or in terms of other clinical or treatment features.

Twenty-one hospitalisations were reported over 35 weeks by 325 patients, yielding a hospitalisation rate of 9.6/100 person-years. Five patients (24%) required oxygen support during hospitalisation and two of them received intensive care. COVID-19 was the reason of admission in none of the 21 hospitalised patients. However, 3/21 hospitalised patients also had COVID-19 during the second observation timeframe (compared to 14/304 among non-hospitalised; $p = 0.088$).

During the second period, one or more symptoms potentially attributable to COVID-19 were experienced by 63% of patients with SLE and 48% of patients' family members/cohabitants, independent of COVID-19 diagnosis. Dry cough, dyspnoea, sore throat, and anosmia or ageusia were significantly more frequent in patients with totCOVID than in patients with noCOVID. Among patients' family members/cohabitants a reported history of COVID-19 (either confirmed by polymerase chain reaction or presumed based on clinical features) was instead significantly associated with fever, dyspnoea, myalgia, anosmia and ageusia (Fig. 2).

3.5. Vaccination attitudes

The median NRS for the estimated likelihood of receiving COVID-19 vaccination was 8 (5–10) out of 10. Consistently, 246 patients (76%) were generally in favour of being vaccinated, although 179 only if prescribed by a Physician and two only if compelled by law. Eighteen of 32 patients not willing to be vaccinated (56%) reported to be worried of experience a lupus flare due to vaccination, while 11/32 expressed

Table 1
Clinical features of responders to the survey by COVID-19 diagnosis and timing of infection.

	Patients with SLE (total)	noCOVID	totCOVID			cCOVID			pCOVID		
			All	First phase	Second phase	All	First phase	Second phase	All	First phase	Second phase
N	334	306	28	12	17	19	4	16	9	8	1
Females: n (%)	301 (90)	274 (90)	27 (96)	12 (100)	16 (94)	18 (95)	4 (100)	15 (94)	9 (100)	8 (100)	1 (100)
Age groups (years): n (%)											
18–25	12 (4)	12 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
26–30	26 (8)	23 (8)	3 (11)	2 (17)	1 (6)	1 (5)	0 (0)	1 (6)	2 (22)	2 (25)	0 (0)
31–35	33 (10)	33 (11)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
36–40	54 (16)	52 (17)	2 (7)	1 (8)	1 (6)	2 (11)	1 (25)	1 (6)	0 (0)	0 (0)	0 (0)
41–45	28 (8)	21 (7)	7 (25)	2 (17)	5 (29)	5 (26)	1 (25)	4 (25)	2 (22)	1 (13)	1 (100)
46–50	43 (13)	38 (12)	5 (18)	2 (17)	3 (18)	3 (16)	0 (0)	3 (19)	2 (22)	2 (25)	0 (0)
>50	138 (41)	127 (42)	11 (39)	5 (42)	7 (41)	8 (42)	2 (50)	7 (44)	3 (33)	3 (38)	0 (0)
Disease duration (years): n (%)											
<2	19 (6)	18 (6)	1 (4)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)	1 (100)
2 to 10	110 (33)	100 (33)	10 (36)	5 (42)	5 (29)	6 (32)	1 (25)	5 (31)	4 (44)	4 (50)	0 (0)
>10	205 (61)	188 (61)	17 (61)	7 (58)	11 (65)	13 (68)	3 (75)	11 (69)	4 (44)	4 (50)	0 (0)
General clinical features: n (%)											
Skin involvement	185 (55)	174 (57)	11 (39)	7 (58)	5 (29)	7 (2)	3 (1)	4 (25)	4 (44)	4 (50)	0 (0)
Joint involvement	243 (73)	222 (73)	21 (75)	9 (75)	13 (76)	14 (74)	3 (1)	12 (75)	7 (78)	6 (75)	1 (100)
Haematological disease	180 (54)	164 (54)	16 (57)	5 (42)	11 (65)	12 (63)	1 (25)	11 (69)	4 (44)	4 (50)	0 (0)
Leukopenia	105 (31)	94 (31)	11 (39)	4 (33)	7 (41)	7 (37)	0 (0)	7 (44)	4 (44)	4 (50)	0 (0)
Thrombocytopenia	95 (28)	88 (29)	7 (25)	1 (8)	6 (35)	7 (37)	1 (25)	6 (38)	0 (0)	0 (0)	0 (0)
Anaemia	84 (25)	78 (25)	6 (21)	1 (8)	5 (29)	5 (26)	0 (0)	5 (31)	1 (11)	1 (13)	0 (0)
Nephritis	123 (37)	115 (38)	8 (29)	3 (25)	5 (29)	6 (32)	1 (25)	5 (31)	2 (22)	2 (25)	0 (0)
NPSLE	52 (16)	49 (16)	3 (11)	3 (25)	0 (0)	1 (5)	1 (25)	0 (0)	2 (22)	2 (25)	0 (0)
Serositis	93 (28)	83 (27)	10 (36)	4 (33)	7 (41)	7 (37)	1 (25)	7 (44)	3 (33)	3 (38)	0 (0)
Constitutional symptoms	317 (95)	292 (95)	25 (89)	11 (92)	15 (88)	18 (95)	4 (100)	15 (94)	7 (78)	7 (88)	0 (0)
Fever	172 (51)	162 (53)	10 (36)	4 (33)	7 (41)	7 (37)	1 (25)	7 (44)	3 (33)	3 (38)	0 (0)
Lymph-node enlargement	138 (41)	121 (40)	17 (61)*	8 (67)	10 (59)	11 (58)	2 (50)	10 (63)	6 (67)	6 (75)	0 (0)
Weight loss	107 (32)	95 (31)	12 (43)	7 (58)	6 (35)	7 (37)	2 (50)	6 (38)	5 (56)	5 (63)	0 (0)
Fatigue	283 (85)	259 (85)	24 (86)	10 (83)	15 (88)	17 (89)	3 (75)	15 (94)	7 (78)	7 (88)	0 (0)
Comorbidities: n (%)											
None	3 (1)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Arterial hypertension	111 (33)	105 (34)	6 (21)	3 (25)	3 (18)	3 (16)	0 (0)	3 (19)	3 (33)	3 (38)	0 (0)
Myocardial infarction	11 (3)	10 (3)	1 (4)	0 (0)	1 (6)	1 (5)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)
Chronic heart failure	4 (1)	4 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Stroke	10 (3)	8 (3)	2 (7)	2 (17)	0 (0)	0 (0)	0 (0)	0 (0)	2 (22)	2 (25)	0 (0)
Diabetes	6 (2)	4 (1)	2 (7)	1 (8)	1 (6)	1 (5)	0 (0)	1 (6)	1 (11)	1 (13)	0 (0)
COPD	6 (2)	5 (2)	1 (4)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	1 (13)	0 (0)
Malignancy	22 (7)	20 (7)	2 (7)	2 (17)	0 (0)	0 (0)	0 (0)	0 (0)	2 (22)	2 (25)	0 (0)
Haematological malignancy	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Asthma	22 (7)	17 (6)	5 (18)*	1 (8)	5 (29)	5 (26)	1 (25)	5 (31)	0 (0)	0 (0)	0 (0)
Any allergy	130 (39)	117 (38)	13 (46)	6 (50)	8 (47)	11 (58)	4 (100)	8 (50)	2 (22)	2 (25)	0 (0)
Drug allergy	89 (27)	81 (26)	8 (29)	4 (33)	5 (29)	7 (37)	3 (75)	5 (31)	1 (11)	1 (13)	0 (0)
Allergy to food, inhalants (pollens, grasses, dustmites…), insect venom	70 (21)	64 (21)	6 (21)	3 (25)	3 (18)	4 (21)	1 (25)	3 (19)	2 (22)	2 (25)	0 (0)
Other	90 (27)	84 (27)	6 (21)	3 (25)	3 (18)	3 (16)	0 (0)	3 (19)	3 (33)	3 (38)	0 (0)
Treatment											
Hydroxychloroquine: n (%)	235 (70)	215 (70)		6 (50)	14 (82)		2 (50)	13 (81)	5 (56)	4 (50)	1 (100)

(continued on next page)

Table 1 (*continued*)

	Patients with SLE (total)	noCOVID	totCOVID			cCOVID			pCOVID		
			All	First phase	Second phase	All	First phase	Second phase	All	First phase	Second phase
			20 (71)			15 (79)					
Prednisone: n(%)	233 (70)	209 (68)	24 (86)	11 (92)	14 (82)	16 (84)	4 (100)	13 (81)	8 (89)	7 (88)	1 (100)
<5 mg/day: n(%)	128 (38)	115 (38)	13 (46)	4 (33)	9 (53)	9 (47)	1 (25)	8 (50)	4 (44)	3 (38)	1 (100)
5 mg/day: n(%)	55 (16)	51 (17)	4 (14)	3 (25)	1 (6)	2 (11)	1 (25)	1 (6)	2 (22)	2 (25)	0 (0)
5–7.5 mg/day: n(%)	32 (10)	28 (9)	4 (14)	2 (17)	2 (12)	3 (16)	1 (25)	2 (13)	1 (11)	1 (13)	0 (0)
7.5–10 mg/day: n(%)	9 (3)	8 (3)	1 (4)	0 (0)	1 (6)	1 (5)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)
10–25 mg/day: n(%)	4 (1)	2 (1)	2 (7)	2 (17)	1 (6)	1 (5)	1 (25)	1 (6)	1 (11)	1 (13)	0 (0)
>25 mg/day: n(%)	5 (1)	5 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Immunosuppressants: n(%)	211 (63)	189 (62)	22 (79)	10 (83)	13 (76)	15 (79)	3 (75)	13 (81)	7 (78)	7 (88)	0 (0)
Azathioprine	45 (13)	37 (12)	8 (29)*	4 (33)	4 (24)	6 (32)	2 (50)	4 (25)	2 (22)	2 (25)	0 (0)
Methotrexate	30 (9)	27 (9)	3 (11)	2 (17)	1 (6)	1 (5)	0 (0)	1 (6)	2 (22)	2 (25)	0 (0)
Mycophenolate mofetil	82 (25)	77 (25)	5 (18)	2 (17)	3 (18)	3 (16)	0 (0)	3 (19)	2 (22)	2 (25)	0 (0)
Cyclosporine A	12 (4)	7 (2)	5 (18)**	4 (33)	2 (12)	2 (11)	1 (25)	2 (13)	3 (33)	3 (38)	0 (0)
Belimumab	52 (16)	46 (15)	6 (21)	3 (25)	3 (18)	3 (16)	0 (0)	3 (19)	3 (33)	3 (38)	0 (0)
Other	95 (28)	87 (28)	8 (29)	2 (17)	6 (35)	6 (32)	0 (0)	6 (38)	2 (22)	2 (25)	0 (0)
Off prednisone and immunosuppressants: n (%)	54 (16)	52 (17)	2 (7)	1 (8)	1 (6)	1 (5)	0 (0)	1 (6)	1 (11)	1 (13)	0 (0)
Treatment changes											
Any escalation: n(%)	97 (29)	84 (27)	13 (46)*	6 (50)	8 (47)	9 (47)	2 (50)	8 (50)	4 (44)	4 (50)	0 (0)
Immunosuppressant	49 (15)	46 (15)	3 (11)	1 (8)	3 (18)	3 (16)	1 (25)	3 (19)	0 (0)	0 (0)	0 (0)
Prednisone	60 (18)	49 (16)	11 (39)*	6 (50)	6 (35)	7 (37)	2 (50)	6 (38)	4 (44)	4 (50)	0 (0)
Belimumab	23 (7)	21 (7)	2 (7)	2 (17)	0 (0)	0 (0)	0 (0)	0 (0)	2 (22)	2 (25)	0 (0)
Any de-escalation: n(%)	114 (34)	103 (34)	11 (39)	4 (33)	7 (41)	8 (42)	1 (25)	7 (44)	3 (33)	3 (38)	0 (0)
Immunosuppressant	40 (12)	35 (11)	5 (18)	1 (8)	4 (24)	4 (21)	0 (0)	4 (25)	1 (11)	1 (13)	0 (0)
Prednisone	78 (23)	72 (24)	6 (21)	3 (25)	3 (18)	4 (21)	1 (25)	3 (19)	2 (22)	2 (25)	0 (0)
Belimumab	3 (1)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

* : $p < 0.05$.
** : $p < 0.010$.

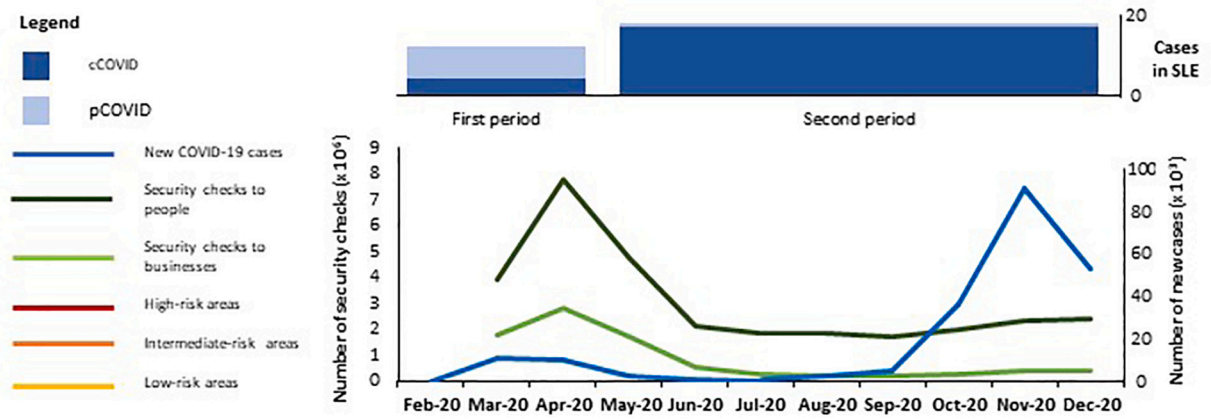
concern about potential side-effects. Five and four patients reported previous adverse reactions to drugs or vaccines respectively as reasons to refuse COVID-19 vaccination. Mass-media were the most frequent source of information about vaccines in responders to the survey (Fig. 3).

4. Discussion

We performed a web-based survey investigating multiple aspects of the ongoing COVID-19 pandemic in a multicentre cohort of patients with SLE, integrated the results with information about the course of the contagion in Italy and validated their reliability against data from patients' charts. Our results show that COVID-19 cases accumulated among patients with SLE throughout 2020, yielding an annual incidence possibly exceeding the one of the general population [12,16,18,21], also in light of underestimation of the impact of fatal or very severe cases (which are reportedly frequent in SLE [22,39]) with our research strategy.

Analysis of individual features associating with the development of COVID-19 showed that having a family member/cohabitant with COVID-19 and being older were major risk factors for infection in patients with SLE, in line with the literature [16]. Furthermore, SARS-CoV-2 infection was associated with unstable disease (either consequent or preceding COVID-19), requiring treatment escalation. Our results also confirm that COVID-like symptoms are frequent in patients with SLE, which might further support the hypothesis of shared mechanisms of aberrant inflammation between COVID-19 and SLE [9].

At a cohort level, we observed a slightly higher number of totCOVID and especially of cCOVID cases in the second half of the year, which included the second pandemic wave. During this second time interval, a higher number of cases was recorded throughout the Country, in parallel with a lower number of checks for the effective application of public health measures. Consistently, relatively looser compliance to behavioural measures was reported by patients and their families along with higher rates of exposure to confirmed COVID-19 cases in the second observation period. Beside infections, the pandemic also affected the routine clinical management of SLE. More than two thirds of patients reported at least one cancelled appointment due to the contagion. Despite this, only 17% of patients felt that the pandemic had a detrimental impact on their disease. Indeed, the reported annual rate of patients needing treatment escalation at least once was 29%, which is stable compared to the pre-pandemic setting [40]. The all-cause annual hospitalisation rate in this study was 9.6/100 person-years, which is also consistent with our preliminary observations during the first pandemic



Activities	0: allowed | 1: allowed with limitations | 2 banned
Travelling within the same municipality	
Travelling within the same region	
Travelling across regions	
Travelling towards alternative properties	
Return to city of residence if in other city	
Gathering in public places	
Ordinary outpatient visits*	
Urgent outpatient visits	
Primary schools	
Secondary schools	
High schools	
University courses	
Medical school courses	
Religious events	
Restaurants	
Large commercial businesses, malls	
Small commercial businesses	
Banks, insurance offices	
Barbers and similar businesses	
All other activities except those involved in logistics, public health or security, primary good supplies, mass media	
Entertainment (cinema, theathres...)	
Public cultural events	
Professional sports	
Non-professional sports	
Training with no range limitations	
Training within 200 m from home	
Access to parks, outdoor recreational activities	
Public transportation	
No need for masks indoor	
No need for masks outdoor	

(caption on next page)

Fig. 1. Population context.
In this figure, the number of cases of confirmed (cCOVID, dark blue) and presumed (pCOVID, pale blue) COVID-19 are depicted in their temporal relation with general population variables, including a) trends of COVID-19 cases in Italy (light blue line); b) trends of security checks to people (dark green line) and businesses (light green line) upon the application of the laws prescribing limitations to gatherings and movements; and c) type and validity of such limitations (table). For each task subject to regulation, a colour-code is applied to distinguish among high- (red), intermediate- (orange) or low-risk (yellow) areas in Italy (the whole Country was homogeneously considered high-risk for almost all the first observation period). Higher-risk colours overlap lower-risk colours where the strictness of a given rule is the same into different risk areas. In addition, rule strictness is graded from 0 (complete freedom) to 2 (complete ban) to generate sparkline graphs for each task. Containment policies were significantly looser in the second observation period. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

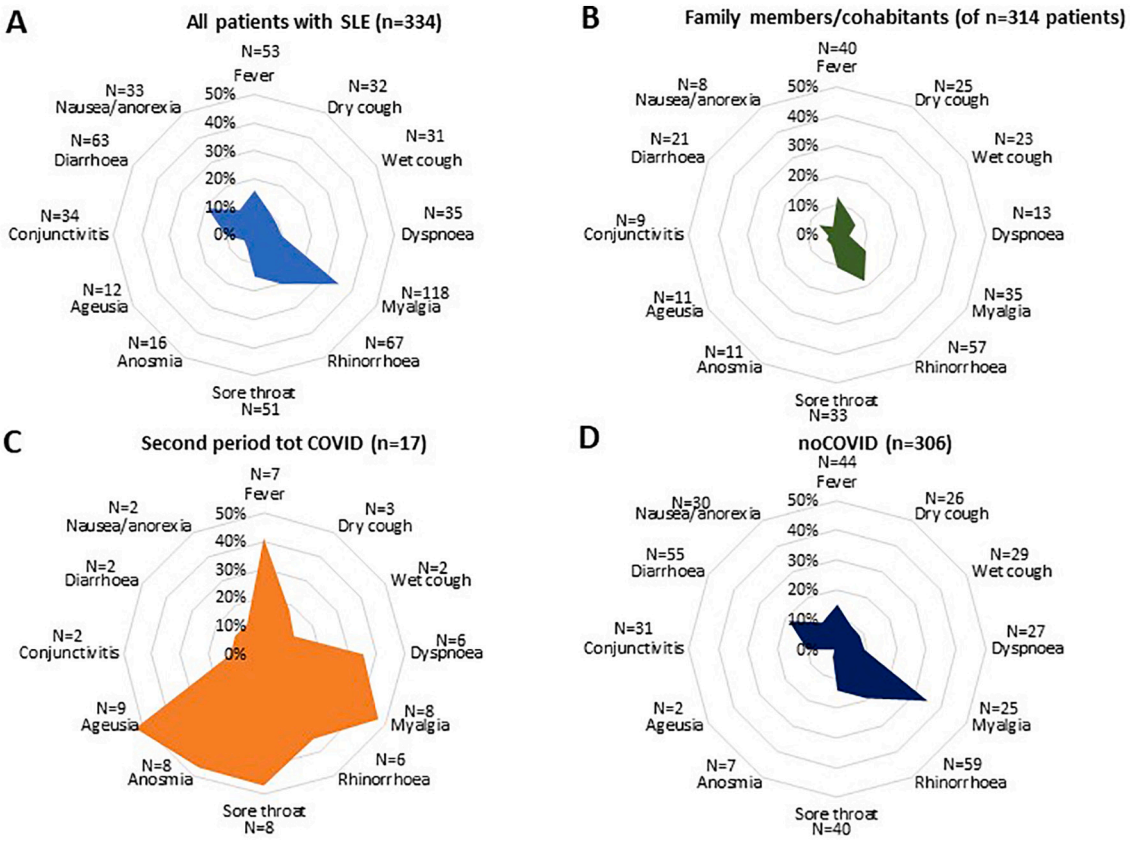


Fig. 2. Symptoms among patients with SLE and their relatives during the second period.
Radar graphs showing the prevalence of COVID-19 related symptoms in patients with SLE (blue) with (totCOVID, orange) or without (noCOVID, dark blue) COVID-19 and their family members/cohabitants. The percentage of symptoms was significantly higher in patients with totCOVID than in patients with noCOVID and in patients with SLE compared to their family members/cohabitants. Dry cough, dyspnoea, sore throat, and anosmia or ageusia were significantly more specifically represented in patients with totCOVID, while myalgia and fever were frequent also in patients with noCOVID. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

wave [21] and previous evidence in the literature from non-pandemic settings [41]. Constant engagement of patients in a multi-centre clinical and research network dedicated to patients with SLE might have contributed to mitigate the detrimental effect of the pandemic [10], besides other potential structural advantages such as relatively easy access to health care, thanks to a public national health system [42]. Efficient individual and population containment measures (with adequate monitoring), such as social distancing, timely lockdowns and extensive vaccination campaigns [43] might further act in synergy [44] and be more relevant than clinical variables such as disease extent and comorbidities in modulating the risk of COVID-19 and its complications in patients with SLE [45–47]. Consistently and in line with previous observations [21,48], patients with SLE tended to be more adherent than their family members/cohabitants to the adoption of behavioural measures. Furthermore, although family members/cohabitants constituted a fundamental source of infection, 68% of patients with COVID-19-positive family members/cohabitants did not develop COVID-19, possibly suggesting that correct awareness of potential risky behaviours positively affects the contagion risk. Data from this study also show that most patients with SLE are favourable to engage in public efforts including vaccination campaigns [49,50] and suggests that cases of vaccine hesitancy might possibly be overcome with adequate counselling.

For a comprehensive interpretation of our results, multiple limitations should be considered. The use of a patient-centred anonymous web-based questionnaire, excluded severely ill or deceased subjects, prevented a full validation of patient-reported information with patients' clinical records and introduced patient's subjectivity as a potential bias to the collection of data from patients' relatives. Furthermore, data from the general population were generated with different methods, warranting caution in comparing them to those of our dataset. On the other hand, our research strategy enjoys the strengths of web-based surveys [3,21,51,52], such as minimising potential biases in the interpretation of patient-reported data and promoting patient engagement in research. In addition, our study is not affected by reporting biases due to the potential selection of most severe cases or by delay in case identification

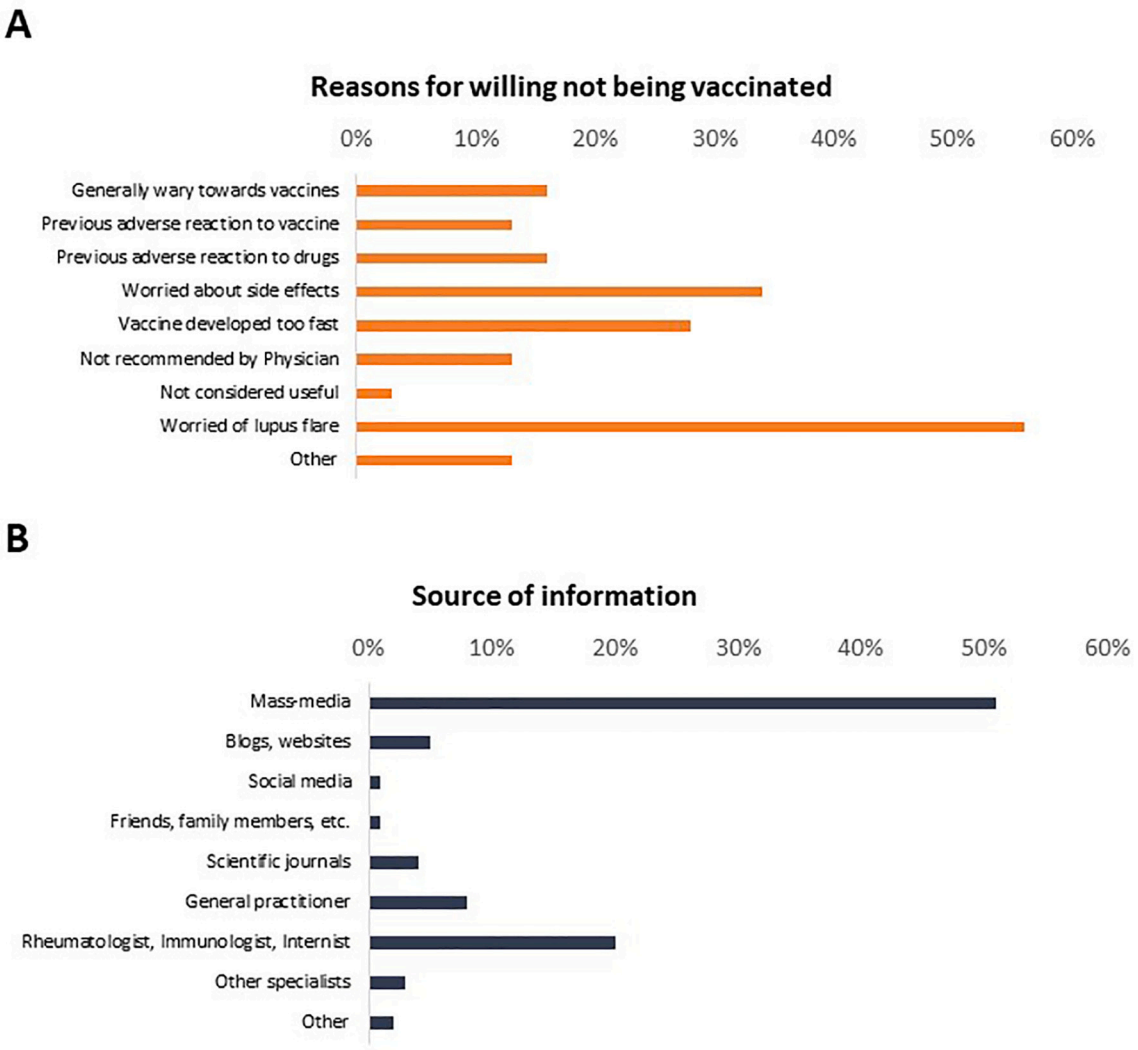


Fig. 3. Reasons for vaccine hesitancy and source of information on vaccines.
This figure summarises the reasons for vaccine hesitancy in 32/325 reporting to be not in favour of being vaccinated (A) and the main sources of information about vaccinations against SARS-CoV-2 among 325 responders to the survey (B).

secondary to cancellation of routine outpatient visits and thus possibly provides complementary information to works based on registries or hospitalisation records [21].

In conclusion, our results suggest that the impact of COVID-19 pandemic on patients with SLE is non-negligible and is significantly modulated by the course of the contagion in the general population. Consistently, similar to the general population, older age and contact with COVID-19 cases within the family setting were major risk factors for infection in our study, although a significant proportion of patients did not develop COVID-19 despite infected subjects in their family. Treatment escalation, especially with corticosteroids, constitutes an additional factor associating with COVID-19 in patients with SLE. Maintenance of strict public health policies to prevent SARS-CoV-2 spread in the population, along with evidence-based, patient-tailored approaches for safe and effective vaccination, might be particularly important to overcome the potential threats posed by the pandemic to the health status of patients with SLE.

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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.

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Conflict of interest statement

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

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