Factors associated with poor outcomes in SLE patients with COVID-19: Data from ReumaCoV-Brazil register

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Abstract

Objectives: To evaluate factors associated with COVID-19 severity outcomes in patients with systemic lupus erythematosus (SLE).

Methods: This was a cross-sectional analysis of baseline data of a prospective, multi-stage cohort study—"The ReumaCoV Brazil"—designed to monitor patients with immune-mediated rheumatologic disease (IMRD) during the SARS-CoV-2 pandemic. SLE adult patients with COVID-19 were compared with those without COVID-19. SLE activity was evaluated by the patient global assessment (PGA) and SLE Disease Activity Index 2000 (SLEDAI-2K).

Results: 604 SLE patients were included, 317 (52.4%) with COVID-19 and 287 (47.6%) in the control group. SLE COVID-19 patients reported a lower frequency of social isolation and worked more frequently as health professionals.
no difference in the mean SLEDAI-2K score between groups in the post–COVID-19 period (5.8 [8.6] vs. 4.5 [8.0]; \( p = 0.190 \)). However, infected patients reported increased SLE activity according to the Patient Global Assessment (PGA) during this period (2.9 [2.9] vs. 2.3 [2.6]; \( p = 0.031 \)). Arterial hypertension (OR 2.48 [CI 95% 1.04–5.91], \( p = 0.041 \)), cyclophosphamide (OR 14.32 [CI 95% 2.12–96.77], \( p = 0.006 \)), dyspnea (OR: 7.10 [CI 95% 3.10–16.23], \( p < 0.001 \)) and discontinuation of SLE treatment medication during infection (5.38 [CI 95% 1.97–15.48], \( p = 0.002 \)), were independently associated with a higher chance of hospitalization related to COVID-19. Patients who received telemedicine support presented a 67% lower chance of hospitalization (OR 0.33 [CI 95% 0.12–0.88], \( p = 0.02 \)).

**Conclusion:** Hypertension and cyclophosphamide were associated with a severe outcome, and telemedicine can be a useful tool for SLE patients with COVID-19.

**Keywords**
COVID-19, SARS-CoV-2, systemic lupus erythematosus, hospitalization

**Key-messages**
- Hypertension were associated with a severe outcome in patients with SLE and COVID-19.
- Cyclophosphamide pulse therapy were associated with a severe outcome in patients with SLE and COVID-19.
- Telemedicine can be a useful tool for patients with SLE and COVID-19.

**Introduction**
Systemic lupus erythematosus (SLE) is a chronic, immune-mediated rheumatologic disease (IMRD), with a two to five-fold higher mortality rate than the general population\(^1,2\) and with infectious complications being responsible for 25%–50% of deaths.\(^3\) The higher risk of infection can be explained by impairment of the immune system, which is inherent to the disease, due to glucocorticoid and immunosuppressant use, and accumulated damage.\(^3,4\) Infections are predominantly bacterial in origin in the community, but there is also an increased risk of fungal, viral, and mycobacterial infections.\(^5-7\)

Since the first cases were described, severe acute respiratory syndrome caused by SARS-CoV-2 infection has become a pandemic, reaching more than 200 countries. Conditions such as systemic arterial hypertension, diabetes mellitus, and chronic kidney disease have been identified as the main risk factors for infection and worse outcomes.\(^8\) Initial studies suggested that autoimmune diseases are not risk factors for COVID-19.\(^8,9\) However, a systematic review published in 2020 reported a higher prevalence of the disease in IMRD, but not in the subgroup of SLE patients.\(^10\) A recent study reported a worse COVID-19 prognosis in IMRD patients, with higher intensive care unit (ICU) admission and mortality rates.\(^11\) The first evaluation of the ReumaCoV-Brazil Registry with 334 IMRD participants showed that being diagnosed with SLE was considered a possible protective factor for ICU treatment.\(^12\)

To date, few studies have described the impact of SARS-CoV-2 infection specifically in SLE patients.\(^9,10,11,13\) In addition to questions regarding the incidence of COVID-19 and outcomes in SLE patients, it is not known whether the infection could induce a disease flare. Both COVID-19 and active SLE can present with cytopenia, arthralgia, myocarditis, interstitial pneumonia, and hemophagocytic syndrome, blurring the distinction between them and making it difficult to define the best therapeutic approach.\(^14,15\)

The main objective of the present study was to evaluate factors associated with COVID-19 severity outcomes in patients with SLE. Additionally, the study evaluated whether SARS-CoV-2 infection was associated with worse SLE activity compared with the group of SLE patients without infection.

**Patients and methods**

**Study design.** This was a cross-sectional study in which patients with SLE (according to the American College of Rheumatology 1997 or Systemic Lupus Erythematosus International Collaborating Clinics 2012 criteria), aged over 18 years, with a diagnosis of COVID-19 were compared to those without COVID-19 included in the ReumaCoV-Brazil Registry.\(^16,17\) ReumaCoV-Brazil is an observational multicenter and prospective cohort still ongoing and includes 43 centers from the five regions of Brazil; its main objective is to monitor adult IMRDs patients with and without a diagnosis of COVID-19. The detailed methodology of the registry has been previously published.\(^18\)

Eligible patients were selected through telephone contact, at outpatient clinics, or during hospitalization related to COVID-19. Patients with a present or previous diagnosis of SARS-CoV-2 infection were classified as
cases. From this total sample, 604 patients with SLE were evaluated: 317 SLE patients with COVID-19 (Group 1) and 287 SLE patients without COVID-19 (Group 2). All patients read and signed the informed consent form before inclusion.

**Data assessment.** Data were collected from the Research Electronic Data Capture platform (RedCap, https://www.project-redcap.org/).

**Patients on the registry are assessed at three time points**

Visit 1: Baseline. Due to local health recommendations related to the SARS-CoV-2 pandemic, the variables collected for before COVID-19 were as described in the medical record at the last presential visit, considering 6 months prior to the diagnosis of SARS-CoV-2 infection. Information related to the post–COVID-19 period was collected at the first face-to-face visit 4–6 weeks after the infection.

Visit 2: 3 months after inclusion (±15 days);
Visit 3: 6 months after inclusion (±15 days).

This study analyzed the data from the first visit of the registry. Demographic data, such as age, sex, work status, and social isolation during the pandemic, as well as data on comorbidities (https://www.who.int/classifications/icd/icdonlineversions/en/), clinical presentations, and SLE treatment were collected. Glomerular filtration rates lower than 29 mL/min/1.73 m² were considered a comorbidity due to kidney disease. Patients were asked whether they had received telemedicine care during COVID-19 infection, for monitoring and treatment of symptoms, or for guidance on warning sings.

Disease activity was assessed through patient global assessment (PGA) and the SLE Disease Activity Index 2000 (SLEDAI-2K). The PGA analysis was based on a visual numeric scale (0–10), with 0 indicating no perception of disease activity and 10, perception of intense activity.

**COVID-19 characteristics and outcomes**

**COVID-19 case definition.** - Patients with an acute respiratory condition characterized by at least two of the following signs and symptoms: fever, dyspnea, cough, sore throat, headache, coryza, olfactory or taste disorders, and/or a detectable SARS-CoV-2 result by reverse transcription polymerase chain reaction (RT-PCR) and/or a reagent result for immunoglobulin (IgM, IgA, and/or IgG).

- Patients with an acute respiratory condition and close contact with a confirmed case of COVID-19 within 14 days prior to the onset of signs and symptoms.

Patients were diagnosed with mild COVID-19 if they required only outpatient care or emergency room care for less than 24 h; moderate in cases of hospital admission; and severe if the patient required intensive care unit care, invasive mechanical ventilation, or in case of death.

**Control group**

Patients with SLE, included in The ReumaCoV-Brazil Registry, without current or previous known COVID-19 infection. **Statistical analysis.** Initially, the study analyzed absolute and relative frequencies of categorical variables as mean (standard deviation), and of numerical variables as median (minimum–maximum values). The normality distribution of numerical variables was analyzed using the Kolmogorov–Smirnov test. Associations between two categorical variables were verified using the chi-square or Fisher’s exact tests.

Comparisons of means between two groups were performed using the Student’s t-test for independent samples. Comparisons of means between more than two groups were performed using the analysis of variance (ANOVA) or the Kruskal–Wallis non-parametric test, according to normality of the variables. Dunn–Bonferroni tests were used to locate differences in the means.

Univariate and multivariate logistic regression models were adjusted to evaluate simultaneous effects of demographic, clinical, and treatment characteristics of the patients with SLE and COVID-19 (predictor variables) on the hospitalization outcome (dependent variable). Variables showing associations with the dependent variable that were significant at 10% in the univariate logistic regression were selected for the multivariable models. Variables that were not significant at 5% were then excluded by order of significance (backward method). The goodness of fit of the final model was assessed using the Hosmer–Lemeshow test. A significance level of 5% was used for all statistical tests.

Data were exported to SPSS statistical software (IBM® SPSS 20.0; IBM Corp., Armonk, NY, USA).

**Results**

In total, 604 patients with SLE were included, 91.6% female with a mean age of 39.7 (12.3) years. In this sample, 226 (37.7%) patients had at least one comorbidity and 160 (26.7%) presented two or more. Regarding medications, 332 (55.0%) patients were using glucocorticoids, 13 (2.15%) methylprednisolone pulse therapy, 514 (85.1%) hydroxychloroquine, and 328 (54.3%) immunosuppressive treatment, including azathioprine (141 [23.3%]), methotrexate (58 [9.6%]), and cyclophosphamide pulse therapy in the last 6 months (18 [3.0%]). Nineteen (3.1%) patients were being treated with belimumab and 14 (2.3%) with rituximab (Table 1).
Table 1. Clinical characteristics of 604 patients with systemic lupus erythematosus with and without COVID-19. Mean (standard deviation).

|                                      | COVID-19 (+) (N = 317) | COVID-19 (−) (N = 287) | P  |
|--------------------------------------|------------------------|-------------------------|----|
| Age (years)a                        | 40.6 (11.9)            | 38.7 (12.1)             | 0.051 |
| Female, n (%)                       | 289 (91.2)             | 264 (92.0)              | 0.718 |
| Profession, n (%)                   |                        |                         | 0.014 |
| Customer service                    | 58 (18.2)              | 53 (18.4)               | –   |
| Health care                         | 32 (10.1)              | 10 (3.4)                | –   |
| Security                             | 8 (2.5)                | 2 (0.6)                 | –   |
| Education                            | 25 (7.8)               | 24 (8.3)                | –   |
| Housewife                            | 86 (27.1)              | 88 (30.6)               | –   |
| Social distancing, n (%)            | 156 (49.5)             | 177/286 (61.9)          | 0.002 |
| Comorbidities, n (%)                 |                        |                         | 0.326 |
| None                                 | 105 (33.1)             | 109 (37.9)              | –   |
| Cardiopathy                          | 19 (5.9)               | 14 (4.8)                | 0.548 |
| Diabetes mellitus                    | 23 (7.2)               | 14 (4.8)                | 0.224 |
| Lung disease                         | 24 (7.5)               | 12 (4.1)                | 0.079 |
| Kidney disease                       | 37 (11.6)              | 45 (15.6)               | 0.150 |
| Systemic arterial hypertension       | 98 (30.9)              | 101 (35.1)              | 0.261 |
| Obesity                              | 49 (15.4)              | 35 (12.1)               | 0.248 |
| Comorbidities, n (%)                 |                        |                         | 0.326 |
| None                                 | 105 (33.1)             | 109 (37.9)              | –   |
| One                                  | 119 (37.5)             | 107 (37.2)              | –   |
| Two or more                          | 91 (28.7)              | 69 (24.0)               | –   |
| Secondary antiphospholipid syndrome  | 33/218 (15.1)          | 21/147 (14.3)           | 0.822 |
| Current smoking, n (%)               | 4 (1.3)                | 10 (3.5)                | 0.073 |
| Abdominal circumference (cm) a       | 94.5 (14.9)            | 90.6 (16.9)             | 0.051 |
| Body mass index (kg/m^2)a            | 28.6 (6.6)             | 27.8 (6.4)              | 0.260 |
| Therapy                              |                        |                         | 0.269 |
| Oral glucocorticoid                  | 181 (57.1)             | 151 (52.6)              | –   |
| Oral glucocorticoid (dosage)         |                        |                         | 0.092 |
| Up to 10 mg/day                      | 116/181 (64.1)         | 104/149 (69.8)          | –   |
| 11–20 mg/day                         | 36/181 (19.9)          | 33 (22.1)               | –   |
| >20 mg/day                           | 29/181 (16.0)          | 12/149 (8.1)            | –   |
| Antimalarials                        | 265 (83.6)             | 249 (86.8)              | 0.276 |
| Azathioprine                         | 76 (24.0)              | 65 (22.6)               | –   |
| Mycophenolate mofoetil               | 51 (16.1)              | 54 (18.8)               | 0.377 |
| Methotrexate                         | 35 (11.0)              | 23 (8.0)                | 0.207 |
| Cyclosporine                         | 2 (0.6)                | 4 (1.4)                 | 0.431 |
| Leflunomide                          | 2 (0.6)                | 3 (1.0)                 | 0.672 |
| Cyclophosphamide pulse therapy       | 11 (3.5)               | 7 (2.4)                 | 0.457 |
| Methylprednisolone pulse therapy     | 7 (2.2)                | 6 (2.1)                 | 0.921 |
| Belimumab                            | 9 (2.8)                | 10 (3.5)                | 0.650 |
| Rituximab                            | 8 (2.5)                | 6 (2.1)                 | 0.724 |
| Disease activity before COVID-19, n (%) |                  |                         | 0.269 |
| PGA (0–10)a                          | 2.5 (2.7)              | 2.4 (2.8)               | 0.011 |
| SLEDAI-2K (range)a                   | 4.6 (7.7)              | 4.9 (8.1)               | 0.764 |
| Absence of activity                  | 53 (16.7)              | 34 (11.8)               | 0.089 |
| Joint                                | 103 (32.5)             | 63 (22.0)               | –   |
| Heart                                | 3 (0.9)                | 13 (4.5)                | 0.006 |
| Cutaneous                            | 84 (26.5)              | 62 (21.6)               | 0.160 |
| Hematological                        | 57 (18.0)              | 33 (11.5)               | 0.025 |
| Pulmonary                            | 10 (3.2)               | 5 (1.7)                 | 0.265 |
(continued)
There were no differences between groups regarding age, sex, disease activity before SARS-CoV-2 infection, and comorbidities (Table 1).

SLE patients with COVID-19 reported a lower frequency of social isolation (49.5% vs. 61.9%; \(p = 0.002\)), worked more frequently as health care professionals (10.4% vs 3.5%; \(p = 0.002\)), and had a higher frequency of joint (32.5% vs. 22.0%; \(p = 0.004\)) and hematologic (18.0% vs. 11.5%; \(p = 0.025\)) manifestations.

Group 1 patients reported feeling increased SLE activity after resolution of COVID-19 symptoms (PGA: 2.9 [2.9] vs. 2.3 [2.6]; \(p = 0.031\)). However, there was no difference in the mean SLEDAI-2K score between groups in the post-COVID-19 period (5.8 [8.6] vs. 4.5 [8.0]; \(p = 0.190\)).

In group 1, 51.1% reported contact with a confirmed case of COVID-19, mainly at home (70%). Only 5% of the patients remained asymptomatic during the infectious period. The most frequent symptoms were headache (58.4%), asthenia (51.7%), and cough (50.5%) (Table 2).

Regarding COVID-19 severity classification, 251 (79.1%) patients were categorized as mild and 66 (20.8%) as moderate to severe. Among 66 patients who were hospitalized, 34.8% required intensive care unit treatment and 28.7% needed invasive mechanical ventilation. Fourteen (21.2%) patients died from COVID-19 complications. The estimated overall deaths attributable to COVID-19, out of the total of 604 SLE patients, were 2.3% (CI 95% 1.3–3.9).

From 59 patients who presented chest computed tomography images, 43 (74%) presented an exam with relevant abnormalities. The main changes were ground-glass opacity with lung parenchyma involvement <50% in 46.5% of the patients, followed by ground-glass opacity with lung parenchyma involvement >50% in 32.6%, and consolidations in 14% of the patients.

In the univariate logistic regression analysis, male sex, older age, the presence of two or more comorbidities, prednisone dose \(\geq 20\) mg/day, and methylprednisolone or cyclophosphamide pulse therapy were associated with hospital admission due to COVID-19. On the contrary, patients who received telemedicine orientation during SARS-CoV-2 infection presented a lower chance of hospitalization (Table 3).

There was no difference in the mean post-COVID-19 SLEDAI-2K score between patients who required and who did not require hospitalization, either in the hospital (4.8 [7.0] vs. 5.9 [8.8], \(p = 0.998\)) or in the intensive care unit (3.7 [3.7] vs. 5.9 [8.7], \(p = 0.936\)).

Cyclophosphamide pulse therapy (OR: 14.32 [2.12–96.77], \(p = 0.006\)), progressing with dyspnea during the infectious episode (OR: 7.10 [3.10–16.23], \(p < 0.001\)), and a history of systemic arterial hypertension (OR: 2.48 [1.04–5.91], \(p = 0.041\)) were independently associated with a greater chance of hospital admission related to COVID-19 (Table 4). Eighty-seven patients who were attended by telemedicine presented a 67% lower chance of hospitalization compared to patients who did not receive this modality of medical evaluation (OR: 0.33 [0.12–0.88], \(p = 0.02\)). The chance of hospitalization was 5.4 times higher in the 32 (10.1%) patients whose SLE treatment medication was discontinued during their SARS-CoV-2 infection; including mycophenolate mofetil, suspended in 11 patients, azathioprine in 10 patients, methotrexate in 10 patients, hydroxychloroquine in 5 patients, cyclophosphamide pulse therapy in 3 patients, and oral corticosteroids in 2 patients.

**Discussion**

SLE patients with COVID-19 reported lower adherence to social distancing and presented a higher frequency of being health care professionals. In addition, patients self-reported more severe disease activity in the period after infectious symptom resolution than the control group, although no difference was observed in SLEDAI-2K. Patients with dyspnea, a history of hypertension, recent treatment with cyclophosphamide and whose SLE treatment medication was discontinued presented worse outcomes regarding COVID-19 severity, demonstrated by a higher frequency of hospital admission.

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**Table 1.** (continued)

|                  | COVID-19 (+) (N = 317) | COVID-19 (−) (N = 287) | \(P\)  |
|------------------|------------------------|------------------------|-------|
| Renal            | 40 (12.6)              | 41 (14.3)              | 0.548 |
| Central nervous system | 22 (6.9)            | 10 (3.5)               | 0.058 |
| Peripheral nervous system | 3/ (0.9)          | 1 (0.3)                | 0.626 |
| Vasculitis       | 9/ (2.8)               | 5 (1.7)                | 0.371 |
| Anti-dsDNA antibodies | 80/164 (48.8)      | 66/125 (52.8)          | 0.498 |
| Positive direct coombs | 23/73 (31.5)     | 14/64 (21.9)           | 0.205 |

**Disease activity post–COVID-19**

- PGA (0–10)\(^a\): 2.9 (2.9) vs. 2.3 (2.6); \(p = 0.031\)
- SLEDAI-2K (range)\(^a\): 5.8 (8.6) vs. 4.5 (8.0); \(p = 0.190\)

GPA: Global Patient Assessment. SLEDAI-2K: modified SLE Disease Activity Index. Antimalarials: hydroxychloroquine/chloroquine diphosphate.
Social distancing is considered one of the main measures to prevent SARS-CoV-2 infection in the general population. To date, there are questions about the role of this sanitary measure associated with other risk factors for viral infection, such as degree of immunosuppression, disease activity, and COVID-19 treatment in patients with IMRDs.

In this cohort, SLE patients with COVID-19 had greater exposure to the virus, but there was no difference in disease activity or immunosuppressive treatment compared with the control group. It is notable that 51.1% of patients with COVID-19 reported contact with a confirmed case, with 70% having occurred at home. Similar results were observed by Ramirez et al. in a study of 417 patients with SLE, 14 with a diagnosis of COVID-19, among whom the inadequate preventive behavior of family members was associated with a greater chance of infection. These preliminary data suggest that measures to prevent SARS-CoV-2 infection in patients with SLE are not different to those recommended for the general population, which include prioritizing the education of patients and family members regarding social distancing, isolation of symptomatic patients, and the use of masks.

Patients with active SLE have a higher risk for infectious complications, which are a trigger for disease activity. However, few studies have evaluated disease activity in patients with SLE after or during SARS-CoV-2 infection. In the present study, SLEDAI-2K was similar between the groups before and after the infectious period; however, the patients with COVID-19 reported a perception of more frequent worsening of SLE activity. In view of these divergent results, two points should be discussed. In the general population, approximately 50%–90% of patients progress with persistent post-acute COVID-19 symptoms, some of which are similar to those reported in several IMRDs. The most frequent symptoms were fatigue.

### Table 2. Presentation and outcomes of COVID-19 in patients with systemic lupus erythematosus.

| Contact with a confirmed case | n (%) |
|------------------------------|------|
| Home                         | 112 (70.0) |
| Work                         | 27 (16.9) |
| Other                        | 21 (13.1) |

| Symptoms | n (%) |
|----------|------|
| Headache | 185 (58.4) |
| Asthenia | 164 (51.7) |
| Cough    | 160 (50.5) |
| Anosmia  | 159 (50.2) |
| Fever    | 147 (46.4) |
| Dysgeusia| 144 (45.4) |
| Coryza   | 139 (43.8) |
| Dyspnea  | 123 (38.8) |
| Myalgia  | 116 (36.6) |
| Diarrhea | 100 (31.5) |
| Arthralgias | 69 (21.8) |
| Nausea   | 66 (20.8) |
| Dizziness| 47 (14.8) |
| Vomiting | 39 (12.3) |
| Skin changes | 16 (5.0) |
| Asymptomatic (only positive lab test) | 16 (5.0) |

| Symptom duration (days)* | 12.1 (8.8) |
| Lab test for SARS-CoV-2 | n (%) |
| RT-PCR                  | 187 (58.9) |
| Serology (IgM/IgG)      | 120 (64.1) |
| Telemmedicine appointment | 67 (35.8) |
| Hospitalization         | 87 (27.4) |
| Intensive care unit admission | 66 (20.8) |
| Invasive mechanical ventilation | 23/66 (34.8) |
| Death                   | 14/66 (21.2) |
| Time from sympton onset to hospital admission* | 7.3 (5.8) |
| Length of hospital stay* | 10.3 (13.2) |

*Mean (standard deviation).
Table 3. Univariate logistic regression considering hospitalization as a dependent variable in SLE COVID-19 patients.

| Variable                                | Crude OR (CI 95%) | p     |
|-----------------------------------------|-------------------|-------|
| **Male**                                | 2.36 (1.03–5.40)  | **0.041** |
| **Age (years)**                         | 1.05 (1.02–1.07)  | **< 0.001** |
| **SLEDAI-2K before COVID-19**           | 0.96 (0.89–1.04)  | 0.304 |
| **SLEDAI-2K before COVID-19**a          |                   |       |
| 3–6                                     | 1.08 (0.37–3.13)  | 0.884 |
| >6                                      | 1.05 (0.34–3.23)  | 0.938 |
| **Social distancing**                   | 1.11 (0.64–1.92)  | 0.715 |
| **Comorbidities**                       |                   |       |
| None                                    | 0.39 (0.20–0.76)  | **0.006** |
| Cardiopathy                             | 4.91 (1.90–12.65) | **0.001** |
| Diabetes mellitus                       | 1.78 (0.70–4.53)  | 0.226 |
| Lung disease                            | 2.07 (0.84–5.07)  | 0.112 |
| Kidney disease                          | 1.52 (0.69–3.32)  | 0.298 |
| Systemic arterial hypertension          | 2.52 (1.44–4.41)  | **0.001** |
| Obesity                                 | 1.32 (0.64–2.70)  | 0.453 |
| **Number of comorbidities**b            |                   | **< 0.001** |
| One                                     | 1.57 (0.73–3.38)  | 0.254 |
| Two or more                             | 4.41 (2.11–9.22)  | **< 0.001** |
| **Current smoking**                     | 3.92 (0.54–28.38) | 0.176 |
| **Abdominal circumference (cm)**        | 1.03 (0.99–1.06)  | 0.135 |
| **Body mass index (kg/m²)**             | 0.99 (0.94–1.05)  | 0.736 |
| **COVID-19 symptoms**                   |                   |       |
| Dyspnea                                 | 4.59 (2.56–8.23)  | **< 0.001** |
| Cough                                   | 1.76 (1.01–3.07)  | **0.047** |
| Coryza                                  | 0.54 (0.30–0.96)  | **0.037** |
| Anosmia                                 | 0.51 (0.29–0.89)  | **0.018** |
| Headache                                | 0.46 (0.26–0.80)  | **0.006** |
| Arthralgias                             | 0.44 (0.20–0.97)  | **0.042** |
| Skin changes                            | 1.83 (0.61–5.45)  | 0.281 |
| Asthenia                                | 0.75 (0.44–1.30)  | 0.313 |
| Diarrhea                                | 0.87 (0.48–1.58)  | 0.653 |
| Fever                                   | 1.58 (0.91–2.73)  | 0.104 |
| Myalgia                                 | 0.79 (0.44–1.41)  | 0.422 |
| Nausea                                  | 0.83 (0.41–1.66)  | 0.600 |
| Dysgeusia                               | 0.70 (0.40–1.22)  | 0.207 |
| Dizziness                               | 1.22 (0.58–2.56)  | 0.594 |
| Vomiting                                | 1.40 (0.64–3.04)  | 0.398 |
| **Symptom duration (days)**             | 1.07 (1.03–1.11)  | **0.001** |
| **Telemedicine care**                   | 0.35 (0.16–0.74)  | **0.006** |
| **Therapy**                             |                   |       |
| Oral glucocorticoids                    |                   |       |
| 0–10 mg/day                             | 1.15 (0.59–2.21)  | 0.685 |
| 11–20 mg/day                            | 1.99 (0.84–4.71)  | 0.116 |
| >20 mg/day                              | 3.66 (1.53–8.72)  | **0.003** |
| Antimalarials                           | 0.65 (0.33–1.28)  | 0.212 |
| Azathioprine                            | 0.94 (0.49–1.79)  | 0.849 |
| Methotrexate                            | 0.844             |       |
| ≤ 20 mg/week                            | 0.88 (0.32–2.42)  | 0.801 |
| > 20 mg/week                            | 1.54 (0.29–8.17)  | 0.609 |
| Mycophenolate mofetil                   | 1.60 (0.80–3.17)  | 0.183 |
| Cyclophosphamide pulse therapy          | 5.02 (1.48–17.02) | **0.010** |

(continued)
dyspnea (43.4%), joint pain (27.3%), and chest pain (21.7%). COVID-19 also progressed with declined functional capacity in 44% of the patients. Persistent COVID-19 symptoms possibly interfered in the self-assessment of patients, either by presenting symptoms similar to those of disease activity or by interfering in their quality of life and, consequently, in their perception of well-being. Another point to consider is the fact that SLEDAI-2k is a global score and frequently underestimates some potentially severe SLE presentations.

COVID-19 symptoms in SLE patients were similar to those reported in the general population, except for the lower frequency of fever (46.6% vs. 88.5%) and higher frequency of headache (58.4% vs. 12.1%). In a Spanish study, 60% of patients with SLE and COVID-19 presented fever, corroborating the results of the present study. The lower frequency of fever in this context can be explained by thermoregulation changes related to glucocorticoid and immunosuppressive treatment.

### Table 3. (continued)

|                          | Crude OR (CI 95%) | p   |
|--------------------------|------------------|-----|
| Methylprednisolone pulse therapy | 10.42 (1.97–55.00) | 0.006 |
| Rituximab                | 0.55 (0.07–4.53)  | 0.576 |
| Belimumab                | 0.48 (0.06–3.88)  | 0.488 |

OR: Odds ratio.  
*Reference: SLEDAI-2K < 3.  
*Reference: none comorbidities Antimalarials: hydroxychloroquine/chloroquine diphosphate.

### Table 4. Multiple logistic regression regarding hospitalization of SLE patients with COVID-19.

|                          | Initial Model | Final Model |
|--------------------------|--------------|-------------|
|                          | Adjusted OR (CI 95%) | p | Adjusted OR (CI 95%) | p |
| Male                     | 2.32 (0.53–10.17) | 0.264 | — | — |
| Age (years)              | 1.02 (0.98–1.06) | 0.278 | 1.04 (1.01–1.07) | 0.045 |
| Comorbidities            |              |           |            |     |
| None                     | 1.45 (0.37–5.64) | 0.589 | — | — |
| Cardiopathy              | 2.29 (0.42–12.38) | 0.336 | — | — |
| Hypertension             | 2.93 (0.95–9.00) | 0.060 | 2.48 (1.04–5.91) | 0.041 |
| Others                   | 1.81 (0.61–5.38) | 0.287 | — | — |
| Symptoms                 |              |           |            |     |
| Arthralgias              | 0.59 (0.18–1.94) | 0.381 | — | — |
| Headache                 | 0.86 (0.3–2.51) | 0.788 | — | — |
| Coryza                   | 0.57 (0.22–1.45) | 0.239 | — | — |
| Dyspnea                  | 8.16 (2.99–22.23) | 0.000 | 7.10 (3.10–16.23) | <0.001 |
| Anosmia                  | 0.52 (0.20–1.37) | 0.185 | — | — |
| Cough                    | 2.11 (0.74–6.01) | 0.161 | — | — |
| Lab test for SARS-CoV-2  |              |           |            |     |
| RT-PCR                   | < 0.001      |           | 1.92 (0.51–7.17) | 0.220 |
| No                       | 2.73 (0.61–12.21) | 0.189 | 15.06 (5.30–42.79) | <0.001 |
| Yes                      | 19.00 (5.61–64.38) | <0.001 | — | — |
| Telemedicine care        | 0.41 (0.14–1.25) | 0.116 | 0.33 (0.12–0.88) | 0.020 |
| Therapy                  |              |           |            |     |
| Oral glucocorticoids     | 0.621         |          | — | — |
| 0–10 mg/day              | 1.70 (0.62–4.61) | 0.300 | — | — |
| 11–20 mg/day             | 1.41 (0.32–6.29) | 0.650 | — | — |
| > 20 mg/day              | 0.66 (0.13–3.36) | 0.620 | — | — |
| Cyclophosphamide pulse therapy | 15.32 (0.75–312.51) | 0.076 | 14.32 (2.12–96.77) | 0.006 |
| Methylprednisolone pulse therapy | 15.59 (0.71–340.33) | 0.081 | — | — |
| Medication discontinuation| 5.39 (1.59–18.25) | 0.007 | 5.38 (1.87–15.48) | 0.002 |

Hosmer and Lemeshow test demonstrated good model adequacy (p = 0.331). OR: odds ratio, CI: confidence interval.
Severe COVID-19 outcomes, such as hospital admission (20.8%), intensive care unit treatment (28.7%), invasive mechanical ventilation (20.8%), and overall mortality (2.3%), were also similar to those reported in the general population.\(^{1,27}\) It is difficult to compare studies evaluating SLE and COVID-19 because these studies are heterogeneous regarding the methodology and characteristics of the study population, especially concerning the disease severity and types of immunosuppressive treatments.\(^{28}\) In the French registry, which compared patients hospitalized with SLE with and without COVID-19, the inpatient mortality rate was 9.5% in the group with COVID-19, four-fold higher than the inpatient mortality of SLE patients hospitalized for other causes.\(^{28}\)

In another study, the hospitalization rate was 82%, with 7% in the intensive care unit, and the mortality rate was 14%, with higher rates than those found in the present study. The factors that may possibly explain the different frequencies of severity outcomes of COVID-19 are glucocorticoid doses, numbers of comorbidities, immunosuppressants, and issues related to infrastructure and access to health.\(^{11,12}\)

Cyclophosphamide treatment in patients with SLE is associated with an increased risk of bacterial and nonbacterial infection, impacting the disease morbidity and mortality.\(^{29}\) In the present study, cyclophosphamide significantly increased hospital admission among patients with COVID-19. Poor control of viral infection by the immune system is one of the main factors contributing to COVID-19 severity, as demonstrated by the association between high viral replication and immune dysregulation.\(^{30}\) Cyclophosphamide is a cytotoxic alkylating medication that interferes with lymphocyte proliferation, reducing the production of effector and cytotoxic T cells, as well as autoantibody production.\(^{31}\) The response of cytotoxic T lymphocytes is crucial for viral eradication in COVID-19. Patients with severe forms of COVID-19 present with perivascular lymphocytic infiltrates and the depletion of almost all T-cell subtypes.\(^{30}\) SARS-CoV-2 infection presents with clonal expansion of plasma cells, producing specific neutralizing antibodies due to multifaceted B-cell activation.\(^{30}\) Cyclophosphamide reduces antibody production, thus also interfering with the humoral response to the virus.\(^{31}\) The COVID-19 Global Rheumatology Alliance also observed worse outcomes in patients with SLE and COVID-19 who were on cyclophosphamide treatment.\(^{32}\)

The present study did not observe worse outcomes in patients treated with rituximab, as reported by some studies.\(^{32-34}\) This fact could be explained by the small number of patients in the study who were being treated with this medication. Data from the Global Rheumatology Alliance with 3729 patients with rheumatic disease and confirmed or presumptive COVID-19 demonstrated that the independent factors associated with COVID-19–related death were age, male sex, hypertension combined with cardiovascular disease, chronic lung disease, and prednisolone-equivalent dosages of ≥10 mg/day. Moderate-to-high disease activity (vs. remission/low disease activity) was associated with higher odds of death as were the use of rituximab, sulfasalazine, and immunosuppressants (e.g., azathioprine, cyclophosphamide, cyclosporin, mycophenolate, or tacrolimus), compared with methotrexate monotherapy.\(^{32}\) The nationwide study in Denmark report that the risk for hospitalization was three-fold higher in SLE patients than the general population, hydroxychloroquine and glucocorticoid treatment was associated with hospitalization.\(^{35}\)

Hypertension is considered a comorbidity associated with worse COVID-19 outcomes.\(^{8,36,37}\) An Italian study evaluated the death certificates of 4691 patients who died because of SARS-CoV-2 infection, showing that hypertension was the most reported comorbidity.\(^{38}\) The prevalence of hypertension in SLE ranges from 9.4% to 77% in several cohorts, depending on the definition used and age group of the studied population. Renal damage secondary to nephritis and glucocorticoid treatment are important causes of hypertension in SLE; however, other mechanisms have been described, such as generalized endothelial dysfunction. Recent studies have also reinforced the role of immune system dysregulation and chronic inflammation in the development and maintenance of hypertension.\(^{39}\) Increased serum concentrations of pro-inflammatory cytokines, such as tumor necrosis factor (TNF) alpha and interleukin-6, were shown to be associated with hypertension.\(^{39}\) Therefore, endothelial dysfunction and immune dysregulation caused by COVID-19 may further intensify the immune imbalance of hypertensive patients with SLE. Aggressive screening and low blood pressure level thresholds for antihypertensive treatment are usual recommendations for SLE patient care, which should be strongly emphasized in the context of the SARS-CoV-2 pandemic.\(^{40}\)

Discontinuation of SLE treatment during COVID-19 infection was associated with hospital admission. This outcome should be carefully analyzed, as the variable encompasses different medications with variable half-life and partial or complete discontinuation. The interference from treatment discontinuation in the immune response to infection could occur either through the reactivation of SLE or by unblocking the specific medication pathway with the release of inflammatory cytokines. Several anti-rheumatic drugs have been involved in the COVID-19 approach, such as tocilizumab in the management of severe forms, anti-TNF showing a protective effect, and rituximab associated with a worse prognosis.\(^{41}\) There is much evidence of a non-protective role of chronic hydroxychloroquine use concerning the severity of COVID-19 in patients with IMRDs.\(^{42}\) Large and longitudinal studies are needed to clarify the influence of both maintenance and
discontinuation of SLE treatment on the severity of COVID-19. Current evidence suggests that disease activity itself is a factor associated with a worse outcome in COVID-19 and the discontinuation of immunosuppressive medications is not recommended, although glucocorticoids should always be used in the lowest possible dose.\textsuperscript{43} The Global Rheumatology Alliance analyses also demonstrated that individuals not receiving treatment for their SLE at the time of COVID-19 diagnosis had poorer outcomes, probably multifactorial, lack of access to SLE care or treatment, or poor adherence with medications.\textsuperscript{32}

Telemedicine, a strategy that enables the provision of medical services remotely and that ensures social distancing, increased exponentially during the pandemic.\textsuperscript{44,45} This tool can help in identifying early signs of severity and in avoiding unnecessary admissions in emergency services, when protocols and adequate health professional training are implemented.\textsuperscript{44} No study to date has evaluated the use of telemedicine in the clinical outcomes of COVID-19, but the use of telemedicine has been fundamental to control the spread of the disease in countries such as China, Australia, and the United States.\textsuperscript{44,46} In this study, patients using telemedicine required less frequent hospital care, thus reaffirming its protective effect on progression to severe outcomes in COVID-19. The study has positive points; it is multicenter, with a significant sample size and inclusion of a control group. The results are also representative because the sample included research centers from the five regions of the country.

The cross-sectional design is the main limitation, and the impossibility of performing the RT-PCR and/or the dosage of immunoglobulin (IgM, IgA, and/or IgG) in all patients with flu-like symptoms at the time of this analysis. Clinical and epidemiologic diagnostic criteria were used because this is a real-life study and, at the time of inclusion, the availability to perform specific test for the diagnosis of COVID-10 was scarce. The inclusion of participants in this study occurred between May and December 2020. At that time, Brazil was in an early phase of the epidemic, but with an increasing incidence and growing mortality rates, ranking fourth in the world for number of cases and sixth in absolute number of deaths. In December 2020, there were 56,773 new cases in 24 h and more than 180,000 deaths from the disease.\textsuperscript{47} The local, social, demographic, and political characteristics must be taken into account to analyze the behavior of the epidemic in Brazil, since the country has a large population, distributed unevenly in the territory, with cultural and geographic differences showing marked social inequalities and access to health services, including access to tests for confirmation of the COVID-19 disease.\textsuperscript{48} The vaccination program only started in January 2021. One year after its beginning, 302.5 million doses were applied, representing 89.3\% of the eligible Brazilian population immunized with the 1st dose and 74.1\% fully vaccinated.\textsuperscript{47}

In conclusion, patients with SLE and COVID-19 engaged less in social isolation, presented more joint and hematological manifestations, used higher doses of prednisone at the moment of COVID-19 infection and reported severe disease activity after infectious by PGA. Cyclophosphamide pulse therapy and a history of hypertension were associated with a higher frequency of hospital admission related to COVID-19. Telemedicine was a useful strategy in these SLE patients. There are still many questions about the influence of SARS-CoV-2 infection on the progression of SLE patients, which can be better answered by longitudinal evaluations. It is also an important goal to characterize immunological deficiencies secondary to SLE, the medications used for SLE treatment, and its comorbidities, which may impair the efficiency of immune responses against SARS-CoV-2. These data reinforce that social isolation policies and care in corticosteroid dosage and judicious use of cyclophosphamide in the management of the disease are necessary.

Acknowledgments

We thank the researchers involved in the centers participating in ReumaCoV-Brasil, the Brazilian Society of Rheumatology and the Conselho Nacional de Desenvolvimento Científico e Tecnológico – CNPq.

Authors’ Contributions

All authors contributed equally in all phases of the protocol design, as well as in the preparation and revision of this manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was funded by the Brazilian Society of Rheumatology, CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico – MCTIC/CNPq/FNDCT/MS/SCTIE/Decit number 07/2020). The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Ethics approval

The results of this research will be presented in an aggregated form, guaranteeing confidentiality and ensuring that there are no risks to patients’ well-being and care. This protocol was approved by the Brazilian Committee of Ethics in Human Research on April 5, 2020 (CAAE 30186820.2.1001.8807; number: 3.933.204), and
registered on the Brazilian Registry of Clinical Trials (RBR-33YTQC) on June 1, 2020.

Data availability statement
The data underlying this article will be shared on reasonable re-
quest to the corresponding author.

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References
1. Abu-Shakra M and Novack V. Mortality and multiple causes of death in systemic lupus erythematosus – role of the death certificate. J Rheumatol 2012; 39: 458–460.
2. Bernatsky S, Boivin JF, Joseph L, et al. Mortality in systemic lupus erythematosus. Arthritis Rheum 2006; 54(8): 2550–2557.
3. Danza A and Ruiz-Iturza A. Infection risk in systemic lupus erythematosus: patients' susceptibility factors and preventive strategies. Lupus 2013; 22(12): 1286–1294.
4. Caza T, Valls Z and Perl A. Interplay of infections, autoimmunity, and immunosuppression in systemic lupus erythematosus. Int Rev Immunol 2014; 33(4): 330–363.
5. Feldman CH, Hiraki LT, Winkelmayer WC, et al. Serious infections among adult Medicaid beneficiaries with systemic lupus erythematosus and lupus nephritis. Arthritis Rheumatol 2015; 67(6): 1577–1585.
6. Ruiz-Iturza A, Oliuares N, Ruiz-Arruza I, et al. Predictors of major infections in systemic lupus erythematosus. Arthritis Res Ther 2009; 11(4): R109.
7. Petri M. Infection in systemic lupus erythematosus. Rheum Dis Clin North Am 1998; 24(2): 423–456.
8. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020; 55(5): 2001227.
9. Liu Y, Sawalha AH and Lu Q. COVID-19 and autoimmune diseases. Curr Opin Rheumatol 2021; 33(2): 155–162.
10. Akiyama S, Hamdeh S, Micic D, et al. Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis. Ann Rheum Dis 2020; 80: 384–391.
11. Xu C, Yi Z, Cai R, et al. Clinical outcomes of COVID-19 in patients with rheumatic diseases: a systematic review and meta-analysis of global data. Autoimmun Rev 2021; 20: 102778.
12. Marques CDL, Kakehasi AM, Pinheiro MM, et al. High levels of immunosuppression are related to unfavourable outcomes in hospitalised patients with rheumatic diseases and COVID-19: first results of ReumaCoV Brasil registry. RMD Open 2021; 7(1): e001461.
13. Espinosa G, Prieto-González S, Llevadot M, et al. The impact of SARS-CoV-2 coronavirus infection in patients with systemic lupus erythematosus from a single center in Catalonia. Clin Rheumatol 2021; 40: 1–7.
14. Borges do Nascimento IJ, von Groote TC, O'Mathúna DP, et al. Clinical, laboratory and radiological characteristics and outcomes of novel coronavirus (SARS-CoV-2) infection in humans: a systematic review and series of meta-analyses. PLoS One 2020; 15(9): e0239235.
15. Conti F, Coccarelli F, Perricone C, et al. Flare, persistently active disease, and serologically active clinically quiescent disease in systemic lupus erythematosus: a 2-year follow-up study. PLoS One 2012; 7(9): e45934.
16. Petri M, Orbai AM, Alarcon GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012; 64(8): 2677–2686.
17. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997; 40(9): 1725.
18. Marques C, Kakehasi AM, Gomides APM, et al. A Brazilian cohort of patients with immuno-mediated chronic inflammatory diseases infected by SARS-CoV-2 (ReumaCoV-Brasil registry): protocol for a prospective, observational study. JMIR Res Protoc 2020; 9(12): e24357.
19. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012; 120(4): c179–e184. DOI: 10.1159/000339789
20. Castrejón I, Tani C, Jolly M, et al. Indices to assess patients with systemic lupus erythematosus in clinical trials, long-term observational studies, and clinical care. Clin Exp Rheumatol 2014; 32(Suppl 85): 85–95.
21. Jolly M, Pickard AS, Block JA, et al. Disease-specific patient reported outcome tools for systemic lupus erythematosus. Semin Arthritis Rheum 2012; 42(1): 56–65.
22. Uribe AG, Vila LM, McGwin G Jr, et al. The Systemic Lupus Activity Measure-revised, the Mexican Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and a modified SLEDAI-2K are adequate instruments to measure disease activity in systemic lupus erythematosus. J Rheumatol 2004; 31(10): 1934–1940.
23. Nussbaumer-Streit B, Mayr V, Dobrescu AI, et al. Quarantine alone or in combination with other public health measures to control COVID-19: a rapid review. Cochrane Database Syst Rev 2020; 4(4): Cd013574.
24. Ramirez GA, Gerosa M, Beretta L, et al. COVID-19 in systemic lupus erythematosus: data from a survey on 417 patients. Semin Arthritis Rheum 2020; 50(5): 1150–1157.
25. Ward MM, Marx AS and Barry NN. Comparison of the validity and sensitivity to change of 5 activity indices in systemic lupus erythematosus. J Rheumatol 2000; 27(3): 664–670.
26. Carfi A, Bernabei R and Landi F. Persistent symptoms in patients after acute COVID-19. Jama 2020; 324(6): 603–605.
27. Zhu J, Ji P, Pang J, et al. Clinical characteristics of 3062 COVID-19 patients: a meta-analysis. J Med Virol 2020; 92(10): 1902–1914.

28. Mathian A, Mahevas M, Rohmer J, et al. Clinical course of coronavirus disease 2019 (COVID-19) in a series of 17 patients with systemic lupus erythematosus under long-term treatment with hydroxychloroquine. Ann Rheum Dis 2020; 79: 837–839.

29. Gladman DD. Indicators of disease activity, prognosis, and treatment of systemic lupus erythematosus. Curr Opin Rheumatol 1994; 6(5): 487–492.

30. Osuchowski MF, Winkler MS, Skirecki T, et al. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. Lancet Respir Med 2021; 9: 622–642.

31. Skare TL, Dagostini JS, Zanardi PI, et al. Infections and systemic lupus erythematosus. Einstein (Sao Paulo) 2016; 14(1): 47–51.

32. Ugarte-Gil MF, Alarcón GS, Izadi Z, et al. Characteristics associated with poor COVID-19 outcomes in individuals with systemic lupus erythematosus: data from the COVID-19 Global Rheumatology Alliance [published online ahead of print, 2022 Feb 16]. Ann Rheum Dis 2022; 81: 970–978. DOI: 10.1136/annrheumdis-2021-221636.

33. Kow CS and Hasan SS. Use of rituximab and the risk of adverse clinical outcomes in COVID-19 patients with systemic rheumatic disease. Rheumatol Int 2020; 40(12): 2117–2118.

34. Loarce-Martos J, García-Fernández A, López-Gutiérrez F, et al. High rates of severe disease and death due to SARS-CoV-2 infection in rheumatic disease patients treated with rituximab: a descriptive study. Rheumatol Int 2020; 40(12): 2015–202135.

35. Cordtz R, Kristensen S, Dalgaard LPH, et al. Incidence of COVID-19 hospitalisation in patients with systemic lupus erythematosus: a nationwide cohort study from Denmark. J Clin Med 2021; 10(17): 3842.

36. Strangfeld A, Schäfer M, Gianfrancesco MA, et al. COVID-19 Global Rheumatology Alliance. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2021; 80(7): 930–942.

37. Wang B, Li R, Lu Z, et al. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. Aging (Albany NY) 2020; 12(7): 6049–6057.

38. Grippo F, Navarra S, Orsi C, et al. The role of COVID-19 in the death of SARS-CoV-2-positive patients: a study based on death certificates. J Clin Med 2020; 9(11): 3459.

39. Sesso HD, Wang L, Buring JE, et al. Comparison of interleukin-6 and C-reactive protein for the risk of developing hypertension in women. Hypertens 2007; 49(2): 304–310.

40. Molina MJ, Mayor AM, Franco AE, et al. Prevalence of systemic lupus erythematosus and associated comorbidities in Puerto Rico. J Clin Rheumatol 2007; 13(4): 202–204.

41. Hyrich KL and Machado PM. Rheumatic disease and COVID-19: epidemiology and outcomes. Nat Rev Rheumatol 2021; 17(2): 71–72.

42. Pinheiro MM, Pileggi GS, Kakehasi AM, et al. Incidence and risk factors for moderate/severe COVID-19 in rheumatic diseases patients on hydroxychloroquine: a 24-week prospective cohort. Clin Exp Rheumatol 2021; 40: 1258–1266.

43. Mehta P, Gasparyan AY, Zimba O, et al. Systemic lupus erythematosus in the light of the COVID-19 pandemic: infection, vaccination, and impact on disease management. Clin Rheumatol 2022; 41: 1–18.

44. Bokolo Anthony J. Use of telemedicine and virtual care for remote treatment in response to COVID-19 pandemic. J Med Syst 2020; 44(7): 132.

45. Timpel P, Oswald S, Schwarz PEH, et al. Mapping the evidence on the effectiveness of telemedicine interventions in diabetes, dyslipidemia, and hypertension: an umbrella review of systematic reviews and meta-analyses. J Med Internet Res 2020; 22(3): e16791.

46. Keshvardoost S, Bahadainbeigy K and Fatehi F. Role of telehealth in the management of COVID-19: lessons learned from previous SARS, MERS, and Ebola outbreaks. Telemed J E Health 2020; 26(7): 850–852.

47. Painel Coronavirus. Secretarias Estaduais de Saúde, Brasil. https://covid.saude.gov.br/ (2020, accessed 20 October 2022).

48. Cavalcante JR, Cardoso-Dos-Santos AC, Bremm JM, et al. COVID-19 in Brazil: evolution of the epidemic up until epidemiological week 20 of 2020. Epidemiol Serv Saude 2020; 29(4): e2020376.