Incidence and risk factors for moderate/severe COVID-19 in rheumatic diseases patients on hydroxychloroquine: a 24-week prospective cohort

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Abstract

Objective

To evaluate the incidence of COVID-19 and its main outcomes in rheumatic disease (RD) patients on hydroxychloroquine (HCQ) compared to household cohabitants (HC).

Methods

This is a 24-week nationwide prospective multi-centre cohort with a control group without RD and not using HCQ. All participants were monitored through scheduled phone interviews performed by health professionals. Details regarding COVID-19 symptoms, and epidemiological, clinical, and demographic data were recorded on a specific web-based platform. COVID-19 was defined according to the Brazilian Ministry of Health criteria and classified as mild, moderate or severe.

Results

A total of 9,585 participants, 5,164 (53.9%) RD patients on HCQ and 4,421 (46.1%) HC were enrolled from March 29th, 2020 to September 30th, 2020, according to the eligibility criteria. COVID-19 confirmed cases were higher in RD patients than in cohabitants [728 (14.1%) vs. 427 (9.7%), p<0.001] in a 24-week follow-up. However, there was no significant difference regarding outcomes related to moderate/ severe COVID-19 (7.1% and 7.3%, respectively, p=0.896). After multiple adjustments, risk factors associated with hospitalisation were age over 65 (HR=4.5; 95%CI 1.35-15.04, p=0.014) and cardiopathy (HR=2.57; 95%CI 1.12-5.91, p=0.026). The final survival analysis demonstrated the probability of dying in 180 days after a COVID-19 diagnosis was significantly higher in patients over 65 years (HR=20.8; 95%CI 4.5-96.1) and with 2 or more comorbidities (HR=10.8; 95%CI 1.1-107.9 and HR=24.8; 95%CI 2.5-249.3, p=0.006, respectively).

Conclusion

Although RD patients have had a higher COVID-19 incidence than individuals from the same epidemiological background, the COVID-19 severity was related to traditional risk factors, particularly multiple comorbidities and age, and not to underlying RD and HCQ.

Key words

rheumatic disease, hydroxychloroquine, COVID-19, SARS-CoV-2, prospective observational cohort, comorbidities, risk factors

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Received on May 10, 2021; accepted in revised form on June 7, 2021.

Competing interests: none declared.

Introduction

The scientific community has been involved in searching for potential treatment for people with COVID-19, as well as preventive measures to mitigate the fast spread during the pandemic (1-4).

Antimalarials, such as, chloroquine (CLQ) and hydroxychloroquine (HCQ) have been widely used for over 70 years in the treatment of malaria and various diseases such as rheumatological conditions, due to their immunomodulatory effect (5). HCQ was one of the drugs considered for treating people ill through infection caused by SARS-CoV-2 or preventing infection in people at risk of getting the disease, such as health workers. Although several observational studies, randomised clinical trials, and systematic reviews have shown a null effect of HCQ on the prevention and treatment of COVID-19 outcomes, there is some uncertainty as to whether patients using it chronically could have more favourable endpoints than non-users (6-11).

Thus, the Brazilian Society of Rheumatology Task Force Against COVID-19 addressed this question through evaluation of the COVID-19 incidence and the main outcomes in RD patients under chronic use of HCQ compared to household cohabitants, in a real-life approach.

Methods

Study design and participants

Details of the protocol design have been described elsewhere (12), entitled the Mario Pinotti II study. Briefly, adult volunteers (≥18 years old) with a previous known diagnosis of RD on HCQ were enrolled in this nationwide multicentre prospective cohort study. Household cohabitants, matched for age and a similar epidemiological background, without RD and not using antimalarials for any purpose, were defined as the control group. All participants were from 22 tertiary rheumatology centres, representing the five Brazilian geographic regions.

RD patients had a medical diagnosis of systemic lupus erythematosus (SLE); rheumatoid arthritis (RA); primary Sjögren syndrome (pSS); systemic sclerosis (SSc); inflammatory myopathies; mixed connective tissue disease; hand osteoarthritis; or Chikungunya-related arthropathy, according to the respective international validated classification criteria (12).

Participants with a history of solid organ or bone marrow transplantation, neoplasm in the previous 12 months, immunoglobulin use in the previous 30 days, current renal replacement therapy, thymus disease, other immunodeficiencies, or positive HIV status were excluded.

This protocol was approved by the Brazilian Committee of Ethics in Human Research – CONEP on March 27th, 2020 (CAAE 30246120.3.1001.5505). The informed consent was conducted by phone, as CONEP waived the requirement for the written informed consent form due to the COVID-19 social distancing constraints. This study was registered at the Brazilian Registry of Clinical Trials (ReBEC; RBR - 9KTWX6). In addition, all sections are in accordance with STROBE guidelines.

Procedures

All participants were monitored through regularly scheduled phone interviews performed by previously trained medical students and physicians. The inclusion period was the first 8 weeks of the SARS-CoV-2 community transmission in Brazil (From 29th, March 2020 to 17th, May 2020). Participants were followed for a further 24 weeks after inclusion (closing visit on 30th, September 2020), with contact twice a month, totalising six visits. At any period of the study, extra visits were performed if any participant reported any symptoms related to COVID-19. More details can be found in the protocol design (12).

Epidemiological and demographic data, as well as clinical characteristics, including comorbidities (such as hypertension, cardiovascular disease, chronic lung disease, chronic kidney disease, and diabetes), self-reported disease activity and concomitant medications, were collected at baseline and at every visit during a 24-week follow-up. Initially, each comorbidity was considered as a categorical variable, and subsequently classified based on the total number (none, 1–2, and more than 3). Glucocorticoids were catego-

rised using current prednisone dosage or equivalent (1–9 mg/day and ≥10 mg/day). In addition, specific information about the COVID-19 symptoms, hospitalisation, need for intensive care, and death was collected in both groups and considered as the main endpoints. All data were stored and managed using an electronic on-line platform (Research Electronic Data Capture – REDCap) [https://www.project-redcap.org/].

Outcome definitions

Participants in this study were defined as having COVID-19, according to the most recent criteria established by the Brazilian Ministry of Health (BMH) during the pandemic period (13) (Fig. 1). Outcomes related to COVID-19 severity were assessed and classified according to the care needed for each patient. Mild COVID-19 required only ambulatory care; moderate COVID-19 required non-intensive hospital treatment; and severe COVID-19 required admission to an intensive care unit (ICU), mechanical ventilation, or led to death (14). All participants were also prospectively monitored during a 24-week follow-up.

Statistical analyses

Descriptive statistics were expressed as mean, standard deviation (SD), frequency (%) and 95% confidence intervals (95% CI). The Kolmogorov-Smirnov test was used to verify a normal data distribution. The chi-square association test was used to assess the association between categorical variables with standardised adjusted residual calculation, or Fisher's exact test for small samples. For the evaluation of clinical variables between two time-points by each group, Wilcoxon non-parametric test and analysis of variance (ANOVA) with repeated measures among scheduled visits were used. In the case of non-normality of data, the means of the groups at each time-point was compared using the Kruskal-Wallis non-parametric test. The comparison between numetest and Mann-Whitney non-parametric test, according to normality distribution. Adjusted multiple linear logistic regression models were performed to assess the simultaneous effects of sex, age, duration of illness, comorbidities, concomitant medications, and other confounding variables, according to group and predefined outcomes. In addition, Cox proportional hazards models adjusted for confounding variables were developed to assess the main outcomes related to survival analysis over time, including log rank and Kaplan-Meier tests.

The time defined as the end date was the date of main outcomes. A *p*-value below 0.05 was considered significant. The statistical analysis was performed using IBM-SPSS v. 21.0 software.

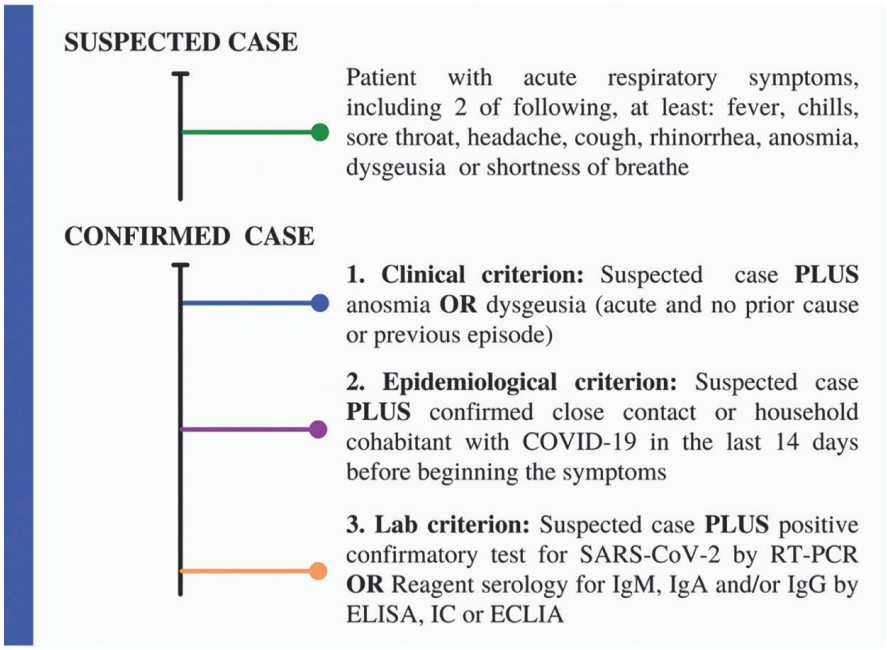

Fig. 1. COVID-19 diagnosis, according to the Brazilian Ministry of Health (BMH) criteria.

Results

At baseline, a total of 9,585 participants were enrolled, according to the eligibility criteria, of whom 5,164 (53.87%) were patients with rheumatic disease on HCQ and 4,421 (46.12%) were cohabitants living with the same epidemiological background (Fig. 2).

In the comparative analysis, the groups were predominantly young with similar age ranges. Patients with RD were predominantly women, had a higher frequency of comorbidities (60.3% *vs.* 38.8%, respectively) and greater adherence to the influenza vaccine. On the other hand, household cohabitants had higher alcohol intake and tobacco exposure (Table I). RD patients were on long-term HCQ with 7.2 (6.2) years and maximum dosage 400 mg (around 5 mg/ kg/ day).

The most frequent RD was SLE (82.2%), followed by RA (7.8%), and pSS (3.7%). Regarding concomitant medications, 1,895 (36.7%) patients were taking GC, 75.7% of them with a daily dosage below 10 mg; current use of DMARDs was reported by half the sample (Table II), especially azathioprine (AZA), mycophenolate mofetil (MMF), and methotrexate (MTX). The mean (SD) of HCQ use time was 7.2 (6.2) years. Rituximab was administered at least once between September 2019 and September 2020, while the doses of belimumab and the other immunobiological agents were routinely maintained.

According to the BMH criteria, the number of COVID-19 confirmed cases during the 24-week follow-up was higher in RD patients on HCQ than in household cohabitants [728 (14.1%) *vs.* 427 (9.7%), $p<0.001$], when clinical and epidemiological criteria were applied. However, there were no statistically significant differences regarding the outcomes related to COVID-19 severity (Table III).

Considering moderate forms, 51 (7.1%) RD patients and 31 (7.3%) cohabitants were hospitalised ($p=0.896$).

The need for an ICU, mechanical ventilation, and death were observed in 12 (23.5%), 7 (58.3%), and 6 (0.8%) RD patients and 9 (29%), 7 (77.8%), and 1 (0.2%) household controls, respectively. However, there were no significant differences between the groups during the 24-week follow-up.

The main risk factors and protective aspects associated with a COVID-19 diagnosis and hospitalisation are shown in Table IV. Interestingly, age presented a bimodal behaviour, according to the endpoint. While younger age was related to a COVID-19 diagnosis, the hospitalisation risk was more associated with age over 65 years. Analysing only the RD patients, the main risk factors associated with a COVID-19 diagnosis were multiple comorbidities and healthcare professionals. On the other hand, the hospitalisation risk was only associated with age over 65 and previous heart disease (Table IV). There was no association among the variables studied and severity outcomes such as the need for ICU, MV, and death considering the global sample and the RD patients (data not shown). Regarding rituximab users, 19 (11.6%) presented COVID-19, with only one hospitalisation and a good outcome. No deaths were reported in this subgroup.

The survival analysis demonstrated that the probability of dying in 180 days after the COVID-19 diagnosis was higher in patients over 65 years (HR=20.8; 95%CI 4.5–96.1, $p<0.001$) and with 2 and 3 or more comorbidities (HR=10.8; 95%CI 1.1–107.9, $p=0.043$ and HR=24.8; 95%CI 2.5–249.3, $p=0.006$ respectively), regardless of underlying rheumatic diseases and HCQ.

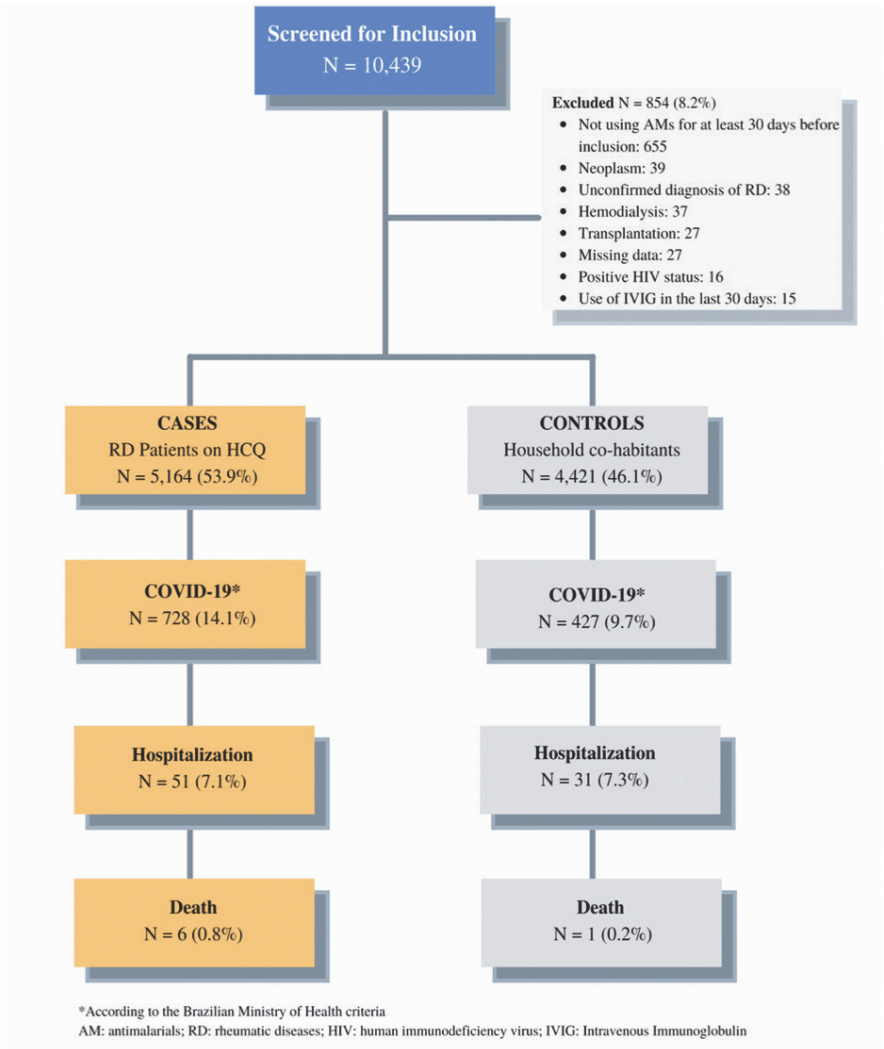

Fig. 2. Study flowchart and outcomes related to COVID-19 in patients with rheumatic diseases on hydroxychloroquine.

Discussion

Our data showed that the probability of a COVID-19 diagnosis was significantly higher in rheumatic disease patients compared to their household controls, regardless of rheumatic disease and the chronic use of hydroxychloroquine. Nonetheless, the risk of developing the moderate-severe forms, including death, was quite similar to cohabitants in this 24-week prospective cohort. In addition, risk factors were also comparable to the general population, especially related to age and multiple comorbidities. The exacerbation rate or flare-up of their underlying rheumatic diseases was also low, suggesting that no additional measures need to be implemented in this scenario beyond maintaining treatment and the universal recommendations to mitigate viral community transmission, including masking, social distancing, hand hygiene, and vaccination.

Our data provide novel evidence demonstrating that chronic use of HCQ is not associated with a reduced incidence of COVID-19. Thus, our data support the current literature addressing a lack of association between HCQ and COVID-19, considering pre-exposure (PrEP). In addition, HCQ post-exposure failed to show any benefit in more recent randomised clinical trials and meta-analysis, including mild-moderate and severe forms of SARS-CoV-2 infection (1, 3, 4, 15-19).

Considering the unmeasurable psychological and emotional burden in many patients with RD and other immunosuppressive conditions, as well as the lack of medical information based on robust clinical studies regarding how to manage them in real-life (20, 21), our prospective data provide relevant knowledge to mitigate fears and uncertainties in dealing with RD patients (1, 22-25, 26-29).

The initial concept was that the inflammatory condition itself and immunosuppressive drugs would be more related to a poor prognosis in RD patients infected by SARS-CoV-2. On the contrary, we found that the traditional risk factors, particularly aging and comor-

Table I. Epidemiological and clinical data between patients with rheumatic diseases and household contacts.

Variables	Total (n=9,585)	Group	
		Patients (n=5,164)	Cohabitants (n=4,421)
Age (years), mean (SD)	43.5 (14.9)	43.1 (13.9)	44.0 (16.1)
Age range, n (%)			
18–64 years	8,740 (90.1)	4,737 (91.7)	3,903 (88.3)
≥65 years	945 (9.9)	427 (8.3)	518 (11.7)
Sex, n (%)			
Female	6,614 (69.4)	4,770 (92.6)	1,844 (42.2)
Male	2,911 (30.6)	382 (7.4)	2,529 (57.8)
Schooling, n (%)			
Illiterate	221 (2.3)	104 (2.0)	117 (2.7)
Elementary school	2,300 (24.1)	1,191 (23.1)	1,109 (25.4)
High school	4,025 (42.2)	2,165 (42.0)	1,860 (42.6)
University education	2,983 (31.3)	1,698 (32.9)	1,285 (29.4)
Profession, n (%)			
Education / housewife	2,297 (24.3)	1,674 (32.7)	623 (14.4)
Customer assistance	1,911 (20.2)	946 (18.5)	965 (22.3)
Healthcare	683 (7.2)	443 (8.7)	240 (5.5)
Security professionals	182 (1.9)	43 (0.8)	139 (3.2)
Other	4,379 (46.3)	2,009 (39.3)	2,370 (54.6)
Current smoking, n (%)	672 (7.1)	250 (4.9)	422 (9.7)
Current alcoholism, n (%)	478 (5.0)	112 (2.2)	366 (8.4)
Comorbidities, n (%)			
Heart disease	496 (5.2)	314 (6.1)	182 (4.1)
Diabetes	703 (7.3)	339 (6.6)	364 (8.2)
Lung disease	497 (5.2)	357 (6.9)	140 (3.2)
Kidney disease	602 (6.3)	565 (10.9)	37 (0.8)
Hypertension	2,673 (27.9)	1,692 (32.8)	981 (22.2)
Others	2,244 (23.4)	1,501 (29.1)	743 (16.8)
Number of comorbidities, n (%)			
none	4,754 (49.6)	2,049 (39.7)	2,705 (61.2)
1	3,071 (32.0)	1,909 (37.0)	1,162 (26.3)
2	1,261 (13.2)	850 (16.5)	411 (9.3)
≥3	499 (5.2)	356 (6.9)	143 (3.2)
Influenza vaccine, n (%)	2,584 (27.2)	1,528 (29.7)	1,056 (24.2)

bidities, could be more involved than specific aspects allied to the rheumatic diseases. Interestingly, we performed a grouping of comorbidities to demonstrate the clinical relevance in identifying patients at a higher risk, since the combination among them demonstrated better performance than each one separately regarding vulnerability and unfavourable outcomes. These findings were clearer over time than during the inclusion period. More recently, a large nationwide study of Danish (30) COVID-19 patients showed a combination of comorbidities through the Charlson Comorbidity Index Score (CCIS) (31) was associated with the risk of a severe outcome and death, after controlling for age and sex.

Of note, almost 40% of our RD patients did not have any comorbidities and 35% had two or more. This finding is similar to current literature reports, demonstrating that the frequency of hypertension and diabetes in RD patients and household controls was comparable to the prevalence in the general population paired by age and sex (around 30% and 8%, respectively) (32, 33), reflecting a real-life setting. Therefore, among RD patients it is essential to identify those with more than one comorbidity to control modifiable risk factors and to reinforce COVID-19 prevention measures. Supporting this, some authors have highlighted the need to develop a specific risk score based on comorbidities to predict severe COVID-19 and death in RD patients (34). Further studies are needed to evaluate if comorbidity combinations could predict poor endpoints in RD patients with COVID-19.

The comparable low frequency of moderate and severe outcomes in RD patients and household controls suggests that our patient population presented predominantly well-controlled diseases, taking into consideration the low daily GC dosage (<10 mg in almost 75% of them) and low proportion of current pulse therapy (around 2% of cyclophosphamide or methylprednisolone) and biologic therapy (around 5%). These findings may account for the more favourable prognosis observed in our patients and contrast with those reported for individuals with high immunosuppression status (35). In addition, it is worth remembering the differing spread velocity of the pandemic among Brazilian centres (36, 37).-

Another important point to note is that the incidence of COVID-19 during the community viral transmission in Brazil was quite similar to the Italian data (Lombardia and Venice) (38-40). Although there are differences regarding the inclusion period and follow-up timing, our data are lower than those reported by Spanish and Chinese authors (29, 41). On the other hand, our data are consistent with a systematic review of 62 observational studies involving a total of 319,025 patients with autoimmune diseases, which demonstrated a COVID-19 prevalence of 0.011 (95% CI 0.005–0.025). In contrast, the meta-analysis of seven case-controlled studies found that the risk was significantly higher than in control patients (OR: 2.19; 95% CI 1.05–4.58, p=0.038). However, the authors pointed out that both outcomes evaluated herein to define severity (hospitalisation: OR=0.35; 95% CI 0.23–0.5 and mortality: OR=0.066; 95% CI 0.036–0.12) were primarily attributed to glucocorticoid use and not to underlying RD (42).

Conventional DMARDs were being used by half of the sample, especially AZA, MMF, and MTX, reflecting the lupus treatment strategy. However, none of them were associated with a higher risk of a COVID-19 diagnosis or unfavourable outcomes. Thus, our data demonstrate the relative safety of maintaining these drugs to control disease activity and to avoid disease flare-ups.

Although lung involvement has been

Table II. Main rheumatic diseases and concomitant medication at baseline.

Rheumatic disease		n (%)
Systemic lupus erythematous		4,241 (82.2)
Rheumatoid arthritis		402 (7.8)
Primary Sjögren syndrome		192 (3.7)
Mixed connective tissue disease		75 (1.5)
Osteoarthritis		66 (1.3)
Systemic sclerosis		43 (0.8)
Inflammatory myopathies		34 (0.6)
Chikungunya		18 (0.3)
Other		93 (1.8)
Concomitant medication related to RD		
Glucocorticosteroids		1,895 (36.7)
	<10 mg/day	1,434 (75.7)
	≥10 mg/day	461 (24.3)
Ibuprofen		35 (0.7)
IV Methylprednisolone (Pulse)		60 (1.2)
Cyclophosphamide (Oral and Pulse)		135 (2.6)
Synthetic conventional DMARDs		4,702 (91.1)
	Azathioprine	1,900 (36.8)
	Mycophenolate mofetil	1,271 (24.6)
	Methotrexate	1,170 (22.7)
	Leflunomide	181 (3.5)
	Cyclosporine	150 (2.9)
	Sulfasalazine	30 (0.6)
Biological or target specific DMARDs		345 (6.6)
	Rituximab	163 (3.2)
	Belimumab	103 (1.9)
	Abatacept	30 (0.6)
	TNF-α inhibitors	27 (0.5)
	Tocilizumab	12 (0.2)
	Tofacitinib	10 (0.2)

Table III. Diagnosis of COVID-19 in patients with rheumatic diseases on hydroxychloroquine and household cohabitants in 24-week follow-up, according to the Brazilian Ministry of Health (BMH) criteria.

COVID-19 confirmed cases		Total (%)	Group		*p**
			RD Patients (%)	Cohabitants (%)	
Global BMH criteria*		1,155 (12.1)	728 (14.1)	427 (9.7)	**<0.001**
Clinical criterion		670 (7.0)	390 (7.6)	280 (6.3)	**0.02**
Lab criterion		194 (2.0)	102 (2.0)	92 (2.1)	0.714
Epidemiological criterion		751 (7.9)	513 (10.0)	238 (5.4)	**<0.001**
COVID-19 severity	Mild	1,072 (92.8)	676 (92.9)	396 (92.7)	0.769
	Moderate	60 (5.2)	39 5.4)	21 (4.9)	
	Severe	23 (2.0)	13 (1.8)	10 (2.4)	

*Confirmed cases of COVID-19: in participants who presented at least one of criteria for the diagnosis of SARS-CoV-2 infection, according to the BMH criteria.

BMH: Brazilian Ministry of Health; RD: rheumatic diseases. Mild COVID-19 required only ambulatory care; moderate COVID-19 required non-intensive hospital treatment; and severe COVID-19 required admission to an intensive care unit (ICU), mechanical ventilation, or led to death. Chi-square association test and Student's t-test.

the main concern in patients with COVID-19, there is accumulating evidence that the disease may cause relevant cardiovascular disturbances. Our data pointed out that pre-existing cardiac involvement (around 6%) was associated with a severe COVID-19 outcome, regardless of underlying RD, HCQ use, and age. Several pathophysiological mechanisms are associated with this complication, including the central role of the angiotensin-converting enzyme 2 (ACE2), the functional receptor for the spike protein of coronaviruses, and highly expressed in cardiomyocytes and alveolar epithelial cells, as well as by acute direct viral injury, myocardial and microvascular dysfunction, hypotension, and hypoxemia, and a virally thrombotic- and inflammatory-induced milieu caused by a hyperinflammatory cytokine storm (43, 44). Thus, monitoring these patients should include serial cardiac troponin and natriuretic peptides, fibrinogen, troponin, D-dimer, and inflammatory biomarkers, as well as an echocardiogram and electrocardiogram (ECG). It is worth emphasising that the cardiac background was not related to HCQ after multiple adjustments in our sample of RD patients. In addition, rheumatologists feel confident to use HCQ routinely in clinical practice without these measurements (5, 45, 46). Although B-cell target therapy in immune-mediated rheumatic diseases was previously associated with a COVID-19 diagnosis (47), we found no cases of moderate-severe outcomes (hospitalisation, mechanical ventilation, or death) in 266 patients using rituximab or belimumab. Our data suggest these therapies could be maintained in RD patients during the COVID-19 pandemic after weighing up the risk/benefit ratio, as well as age, comorbidities, disease activity, risk of flare-up, and need for increasing corticosteroids in a personalised approach.

Considering the great challenge for rheumatologists since the beginning of pandemic, our data bring a robust result about one of therapeutic armamentarium currently employed in the management of systemic autoimmune rheumatic diseases (48-50). To the best of our knowledge, this is the largest prospective epidemiological study designed to evaluate the preventive role of chronic use of HCQ in the incidence and severity of COVID-19 in RD patients over time. In addition, some strengths should be considered, such as the sample size, control group with the same epidemiological setting, weekly data quality monitoring, and the use of a specific platform to collect all the information using serial and predetermined and scheduled telephone calls during the follow-up, with national representation in pandemic times. It is important to note that the healthcare professional evaluators remained the same throughout the follow-up. Furthermore, the BMH criteria for COVID-19 have several similarities with the US criteria to define COVID-19 (51). In addition,

Table IV. Final logistic regression multivariate model showing the risk factors associated with COVID-19 diagnosis and hospitalisation after 24 weeks of follow-up, considering the total sample (n=9,589) and only the patients with rheumatic diseases on hydroxychloroquine (n=5,164).

Risk factors considering total sample*	Outcomes (OR; 95%CI)	
	COVID-19 diagnosis	Hospitalisation
Age over 65 years	0.29 (0.2-0.4), $p<0.001$	3.27 (1.43-7.48), $p=0.005$
Male sex	0.78 (0.65-0.94), $p=0.008$	
Any rheumatic disease	1.28 (1.06-1.49), $p=0.002$	
Individuals working with healthcare	2.38 (1.90-2.96), $p<0.001$	
Individuals working with security services	1.78 (1.14-2.78), $p=0.012$	
Lung disease	1.40 (1.09-1.81), $p=0.009$	
Kidney disease	1.33 (1.06-1.67), $p=0.015$	
Risk factors for only RD patients**	**Outcomes (OR; 95%CI)**	
	COVID-19 diagnosis	Hospitalisation
Age > 65 years	0.18 (0.10-0.32), $p<0.001$	4.50 (1.35-15.04), $p=0.014$
Healthcare professionals	2.13 (1.63-2.78), $p<0.001$	
Lung disease	1.45 (1.08-1.94), $p=0.013$	
Kidney disease	1.29 (1.01-1.63), $p=0.03$	
Heart disease		2.57 (1.12-5.91), $p=0.026$
Rituximab	1.87 (1.10-3.17), $p=0.021$	

*Multivariate logistic regression models adjusted for age, sex, underlying rheumatic disease, influenza vaccine, schooling, profession, diabetes, lung disease, kidney disease.
**Multivariate logistic regression models adjusted for age, sex, schooling, profession, influenza vaccine, lung disease, kidney disease, rituximab, oral glucocorticosteroids.

our data have external validity because they included telemedicine during social distancing, individuals from different demographic, social, and economic clusters, including family income, education background, regions, and professions (presential and work from home activities), as well as a real-life scenario.

Our study has some limitations that are inherent to the COVID-19 pandemic, including the need for social distancing and specific guidance for the patients to avoid seeking medical care unless necessary. Data were therefore restricted to self-reported data, including information on disease activity. In addition, there was a small number of confirmatory lab tests (RT-PCR and serology) in the first epidemiological weeks. Another limitation was the lack of patients with RD not using HCQ as another control group. However, this approach could present other prescription biases, as SLE patients without antimalarial treatment are quite uncommon. The strategy of prioritising and enrolling the household cohabitants was chosen because of the relevant epidemiological impact of COVID-19. In addition, the control group was chosen as they share the same epidemiological background (cohabitants living in the same place and paired for age). Expectedly, RD patients had a higher frequency of comorbidities, except diabetes. On the other hand, the control group, made up of family members, usually husbands more frequently reported lifestyle habits related to non-transmissible chronic diseases, such as smoking and alcohol intake.

Therefore, our data provide significant evidence of a non-protective role of chronic HCQ use concerning the incidence and severity of COVID-19 in RD patients. Furthermore, our results highlight the relevance of aging (52, 53) itself and comorbidities considered together, regardless of underlying rheumatic disease and immunosuppression therapy, to manage RD patients during the COVID-19 pandemic in clinical practice.

Acknowledgments

We are grateful to the *Brazilian Society of Rheumatology* for technical support and rapid nationwide mobilisation; to all the 395 interviewers (medical students and physicians) from 22 Rheumatic Diseases Academic Centres who collaborated in the study and the participants; to the Brazilian Ministry of Health and to the Science, Technology, Innovation and Strategic Resources Department (DECIT - Departamento de Ciência, Tecnologia, Inovação e Estratégia de Recursos), to the REDCap for providing fast and feasible platform support; and to the National Council for Scientific and Technological (CNPq - Conselho Nacional de Desenvolvimento Científico e Tecnológico), grant no.: 306879/2018-2.

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