Effect of chronic hydroxychloroquine use on COVID-19 risk in patients with rheumatoid arthritis and systemic lupus erythematosus: a multicenter retrospective cohort

Ismail A. Walbi1, Hassan A. Albarqi2, Nayef Saleh Alghanim3, Marzooq Abdullah Albadi4, Hesham Mohammed Al Maimouni5,6, Saad Ahmed Alkahtani1, Ali Mohamed Alshabi1, Amer S. Alali7, Faleh Alqahtani8, Amal Hassan Al-Najjar9, Mohammad A Hazzazi6,10, Deemah S Alanazi11, Abdulrahman Abdulaziz Sabei12, Omer S Alsaweed13, Rahaf K Alajra13 and Hussain Alqhtani1*

1Department of Clinical Pharmacy, College of Pharmacy, Najran University, Najran, Saudi Arabia
2Department of Pharmaceutics, College of Pharmacy, Najran University, Najran, Saudi Arabia
3Consultant, Rheumatology Department, King Saud Medical City, Riyadh, Saudi Arabia
4Consultant internist and rheumatologist, Security Forces Hospital Program, Riyadh, Saudi Arabia
5Consultant, Rheumatology, Division of Rheumatology, Department of Medicine, King Abdulaziz Medical City, Riyadh, Saudi Arabia
6Assistant Professor of Medicine, King Saud Bin Abdulaziz University of Health Sciences, Ministry of National Guard Health Affairs, Riyadh, Kingdom of Saudi Arabia
7Department of Pharmaceutics, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-kharj, 11942, Saudi Arabia
8Department of Pharmacology and Toxicology, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia
9Drug & Poison Information Center Supervisor, Security Forces Hospital Program, Riyadh, Saudi Arabia
10Vitreoretinal Division, Department of Vitreoretinal, King Abdulaziz Medical City, Riyadh, Saudi Arabia
11Senior Pharmacist, Pharmaceutical Care Services, King Saud Medical City, Riyadh, Saudi Arabia
12Senior Registrar, Ministry of Health, First Health cluster, Western Riyadh Dental Complex, Periodontic Division, Riyadh, Saudi Arabia
13Laboratory Services, Security Forces Hospital Program, Riyadh, Saudi Arabia

*Corresponding author:
Hussain Alqhtani, Department of Clinical Pharmacy, College of Pharmacy, Najran University, King Abdulaziz Road P.O. Box 1988, Najran, Saudi Arabia.
Email: hmhalqhtani@nu.edu.sa

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
Abstract
Objective: Hydroxychloroquine (HCQ) has been used during the coronavirus disease 2019 (COVID-19) pandemic because of its reported anti-viral activity. This study examined the association of chronic HCQ use with the incidence and complications of COVID-19.

Methods: This retrospective cohort study included adults with rheumatoid arthritis and/or systemic lupus erythematosus who visited rheumatology clinics in three tertiary hospitals in Riyadh, Saudi Arabia between January 2019 and December 2020. Patients were categorized into two groups based on HCQ use. Data were obtained from the electronic health record and by interviews with patients. The primary study objective was the incidence of COVID-19 and its complications from March 2020 to February 2021.

Results: Almost 11% of the study cohort was positive for COVID-19, and the incidence of COVID-19 was similar between HCQ users (11.11%) and nonusers (10.86%). Disease complication rates were similar in the study arms, and they mainly included fever, dry cough, fatigue, and breathing difficulty.

Conclusions: This study revealed no significant association between chronic HCQ use and the incidence of COVID-19, and disease complications were similar in the study arms.

Keywords
Hydroxychloroquine, coronavirus disease 2019, disease complication, rheumatoid arthritis, systemic lupus erythematosus, severe acute respiratory syndrome coronavirus-2, chronic drug use, drug repurposing

Date received: 17 November 2021; accepted: 10 March 2022

Introduction
Although the coronavirus disease 2019 (COVID-19) vaccine is being distributed globally, a need for effective therapies remains, especially in areas in which vaccination uptake is slow and vaccine escape because of mutations is possible. Because the urgency of the pandemic makes the development of novel medications nearly impossible, repurposing existing drugs to treat COVID-19 is an appealing strategy, particularly for drugs that are already licensed for other indications and that have well-established safety profiles. In early 2020, hundreds of drugs were trialed in mostly hospitalized patients with COVID-19, generating a massive amount of data of varying quality. To some extent, global guidance is based on these data. For example, UK guidelines recommend that patients who require supplemental oxygen should be given dexamethasone or tocilizumab according to the patient need. Remdesivir has been conditionally recommended for adults with COVID-19 pneumonia who are on supplemental oxygen but not on mechanical ventilation. Data from clinical trials that examined multiple medications are also crucial for eliminating drugs without proven efficacy against COVID-19. Although only 1 of 18 randomized trials demonstrated a benefit, hydroxychloroquine (HCQ) has been administered to roughly one in every three patients with COVID-19 globally. Some studies revealed its effectiveness in preventing thromboembolic events.
Conversely, several previous studies, as reviewed in a recent review, revealed inconsistent anti-COVID-19 effects of HCQ, and no convincing efficacy was recorded in the majority of retrospective and observational trials. HCQ is an anti-malarial drug used extensively in the treatment of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) because of its immunomodulatory effects. In vitro studies demonstrated that HCQ effectively inhibits severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as pretreatment of Vero cells with HCQ inhibited SARS-CoV-2 replication. However, HCQ did not exert anti-SARS effects in well-conducted trials. SARS-CoV-2 can be inhibited by HCQ by affecting viral entry and post-entry processes. The drug impacts the formation of sialic acid moieties in angiotensin-converting enzyme 2 (ACE2) and the terminal glycosylation of S protein by blocking glycosylation, diminishing the interaction between ACE2 and S protein. A ganglioside-binding domain is found at the N-terminus of S protein. This domain binds to sialic acid residues on GM1 ganglioside cell surface receptors, allowing it to attach to ACE2 more easily. The entrance of SARS-CoV-2 into cells is further inhibited by HCQ, which binds to these gangliosides with high affinity. HCQ concentrates in acidic lysosomes and endosomes because it is a weak base. The drug prevents endosomal maturation and the fusion of viral and endo-lysosomal membranes by increasing endosomal pH. It also reduces the activity of endo-lysosomal cathepsins through the same mechanism. The immunomodulatory action of HCQ is believed to play a role in its effects because it inhibits MHC class II expression, the production of pro-inflammatory cytokines such as IL-1, and TNF-α and TLR signaling. Although this is only a hypothesis, this anti-inflammatory activity could counteract the cytokine flood that causes severe COVID-19 and minimize infection severity.

The US Food and Drug Administration (FDA) issued an emergency use authorization (EUA) in March 2020 permitting the distribution of HCQ to certain hospitalized patients with COVID-19. In June 2020, the FDA revoked this EUA based on scientific data illustrating that HCQ is unlikely to be effective in treating COVID-19 for the authorized uses. HCQ was initially proposed to represent an effective, safe, and affordable drug to control the COVID-19 pandemic globally. However, it is crucial to determine whether HCQ prevents or reduces the risk of COVID-19 or its complications, especially in chronic users. The primary chronic users of HCQ are patients diagnosed with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Assessing the impact on such patients during the current pandemic will provide clues regarding the effectiveness of HCQ in preventing COVID-19 or reducing its complications. The main objective of this study was to investigate the association between chronic HCQ use and the incidence of COVID-19 and its effects on disease complications in Saudi Arabia.

Materials and methods

Study design and population

A retrospective cohort study was conducted to compare the outcomes of patients with COVID-19 and coexisting RA and/or SLE according to the use of HCQ. This multicenter, retrospective cohort study was performed in three tertiary hospitals in Riyadh, Saudi Arabia: Security Forces Hospital, King Saud Medical City, and King Abdulaziz Medical City -National Guard. The design and reporting of this study conform to STROBE and EQUATOR guidelines.
Ethical approval for this study was received from the Institutional Review Board of King Saud Medical City (protocol/serial number: H-01-R-053, IORG 0010374, H1R1-21-Jun20-05; approval date: 6 July 2020; approval date: 8 July 2020), Security Forces Hospital (protocol/serial number: H-01-R-069, 20-434-46; approval date: 1 October 2020), and King Abdullah International Medical Research Center (serial number: RC20/440/R). Informed consent was obtained verbally from the subjects involved in this study during the phone interviews.

Data source

The study was conducted using the electronic health record (EHR) of each aforementioned hospital. The databases contain enrollment data (sociodemographic information including age, sex, and geographic region), smoking status, medical history files (including inpatient admission records, outpatient visits, outpatient prescription drug claims, and facility), and patient medication records (including generic name, quantity, strength, date the prescription was filled, days of supply, patient identification number, date of birth, sex, and provider identification number). It also includes supplemental databases on subgroups, such as the results of outpatient laboratory tests.

Data were extracted for patients who visited rheumatology clinics at these hospitals and received a diagnosis of RA/SLE between January 2019 and December 2020. Patients with RA/SLE were categorized as HCQ chronic users when they used the drug for at least 1 month. All patients were required to have at least two diagnoses of RA/SLE and to have received a cortisone or disease-modifying anti-rheumatic drug (DMARD)/anti-SLE prescription. Patients not meeting these criteria and those with less than 1 year of follow-up, those with duplicate data, and those who refused to participate were excluded.

Statistical analysis

Descriptive statistics were used to describe all available variables. Continuous variables were reported as the mean ± standard deviation, and categorical variables were reported as proportions. Categorical variables were compared between HCQ users and nonusers using the chi-square test. For continuous variables, t-tests were used to compare study groups. A logistic regression model was used to identify independent predictors of HCQ use among patients with RA/SLE.

Propensity score matching and inverse probability of treatment weighting analyses with age, sex, smoking, region, presence of RA or SLE, education level, diabetes mellitus, hypertension, and corticosteroid use as covariates were used to account for relevant confounders and adjust for differences between HCQ users and nonusers. Logistic regression analysis was used to assess the odds ratio (OR) for COVID-19 events between HCQ users and nonusers. We further performed sensitivity analyses for disease type to ensure the robustness of our analysis model. All analyses were conducted with an a priori significance level.
level of 0.05 and performed using SAS version 9.4 (SAS Institute Inc., version 9.4, Cary, NC, USA).

Results

Among 691 patients with RA/SLE who visited rheumatology clinics in three tertiary hospitals in Riyadh, Saudi Arabia between January 2019 and December 2020, we excluded 180 patients because they refused to participate in the study, they had duplicate records, they had an observation period shorter than 1 year and fewer than 6 months of follow-up after the study index date, they lacked an RA/SLE diagnosis, or they were younger than 18 years old (Figure 1). The remaining 511 patients were divided into two groups: HCQ users (N = 304, 59.5%) and HCQ nonusers (N = 207, 40.5%).

The clinical and demographic characteristics of these groups are presented in Table 1. In total, 325 patients (63.6%) were diagnosed with RA, 151 patients (29.55%) were diagnosed with SLE, and 35 (6.85%) were diagnosed with both diseases. The mean age of the enrolled patients was 44 years, and more than 80% of patients were female. Meanwhile, smoking was reported for only 7.83% of study participants. Most of the study cohort lived in the central region (86.89%), and they had been diagnosed with RA/SLE at least 2 years prior to enrollment (84%). More than 37% of the study cohort had a college degree. More than 15% of the study cohort had a history of diabetes mellitus, 20% had hypertension, and more than 27% had a history of corticosteroid use.

Table 2 highlights the predictors of HCQ initiation among patients with RA/SLE.
Table 1. Baseline patient characteristics of patients with RA and/or SLE in Saudi Arabia.

|                          | Study cohort | HCQ users | HCQ nonusers |
|--------------------------|--------------|-----------|--------------|
|                          | N  | %    | N  | %    | N  | %    |
| Total                    | 511| 100  | 207| 40.51| 304| 59.49|
| Diagnosis                |    |      |    |      |    |      |
| RA                       | 325| 63.60| 191| 92.27| 134| 44.08|
| SLE                      | 151| 29.55| 14 | 6.76 | 137| 45.07|
| RA and SLE               | 35.00| 6.85 | 2  | 0.97 | 33 | 10.86|
| Age, mean (median)       | 44.5 (44)   | 47 (48)  | 43 (42) |
| Sex                      |    |      |    |      |    |      |
| Male                     | 92 | 18   | 51 | 24.64| 41 | 13.49|
| Female                   | 419| 82   | 156| 76.36| 263| 86.51|
| Smoking                  |    |      |    |      |    |      |
| Yes                      | 40 | 7.83 | 27 | 13.04| 13 | 4.28 |
| No                       | 471| 92.17| 180| 86.96| 291| 95.72|
| Region                   |    |      |    |      |    |      |
| Central                  | 444| 86.89| 185| 89.37| 259| 85.20|
| North                    | 20 | 3.91 | 6  | 2.90 | 14 | 4.61 |
| South                    | 31 | 6.07 | 13 | 6.28 | 18 | 5.92 |
| West                     | 11 | 2.15 | 2  | 0.97 | 9  | 2.96 |
| East                     | 5  | 0.98 | 1  | 0.48 | 4  | 1.32 |
| Education                |    |      |    |      |    |      |
| <High school             | 175| 34.25| 87 | 42.03| 88 | 28.95|
| High school              | 126| 24.66| 55 | 26.57| 71 | 23.36|
| College degree           | 190| 37.18| 61 | 29.47| 129| 42.43|
| Graduate degree          | 20 | 3.91 | 4  | 1.93 | 16 | 5.26 |
| Diagnosis date           |    |      |    |      |    |      |
| <6 months                | 12 | 2.36 | 4  | 1.95 | 8  | 2.63 |
| 6–12 months              | 28 | 5.50 | 11 | 5.37 | 17 | 5.59 |
| 12–24 months             | 41 | 8.06 | 19 | 9.27 | 22 | 7.24 |
| >24 months               | 428| 84.09| 171| 83.41| 257| 84.54|
| Comorbidities/medications|    |      |    |      |    |      |
| Diabetes mellitus        | 78 | 15.26| 47 | 22.71| 31 | 10.20|
| Hypertension             | 105| 20.55| 53 | 25.60| 52 | 17.11|
| Thyroid disease          | 78 | 15.26| 29 | 14.01| 49 | 16.12|
| Coronary disease         | 24 | 4.70 | 11 | 5.31 | 13 | 4.28 |
| Respiratory disease      | 44 | 8.61 | 19 | 9.18 | 25 | 8.22 |
| Corticosteroids          | 138| 27.01| 26 | 12.56| 112| 36.84|
| Anti-hypertensive agents | 37 | 7.24 | 22 | 10.63| 15 | 4.93 |
| Anti-diabetic agents     | 16 | 3.13 | 14 | 6.76 | 2  | 0.66 |
| Anti-coagulants          | 22 | 4.31 | 4  | 1.93 | 18 | 5.92 |
| NSAIDs                   | 17 | 3.33 | 2  | 0.97 | 15 | 4.93 |
| Vitamins                 | 35 | 6.85 | 8  | 3.86 | 27 | 8.88 |

Fisher’s exact test was applied when the sample size was less than 5.
RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; NSAID, nonsteroidal anti-inflammatory drug; HCQ, hydroxychloroquine.
Younger patients were more likely to receive HCQ, and female patients had greater odds of HCQ treatment (OR = 2.10, 95% confidence interval [CI] = 1.33–3.31, P = 0.0005). Patients with an undergraduate (OR = 2.09, 95% CI = 1.37–3.19, P = 0.0007) or graduate degree (OR = 3.95, 95% CI = 1.27–12.30, P = 0.018) had greater odds of HCQ treatment than those with less than a high school education. Patients with a history of diabetes mellitus (OR = 0.39, 95% CI = 0.24–0.63, P = 0.0002) or hypertension (OR = 0.60, 95% CI = 0.39–0.92, P = 0.020) had lower odds of HCQ treatment. Furthermore, patients with a history of corticosteroid, anti-hypertensive drug, anti-diabetic drug, anti-coagulant, nonsteroidal anti-inflammatory drug.

Table 2. Predictors of hydroxychloroquine use among patients with rheumatoid arthritis and systemic lupus erythematosus in Saudi Arabia.

| Predictor                        | Adjusted odds ratio | 95% confidence interval | P   |
|----------------------------------|---------------------|-------------------------|-----|
| **Demographics**                 |                     |                         |     |
| Age                              | 0.976               | 0.96                    | 0.99| 0.0005 |
| Sex                              |                     |                         |     |
| Male                             | –                   | –                       | –   | –      |
| Female                           | 2.10                | 1.33                    | 3.31| 0.0015 |
| **Region**                       |                     |                         |     |
| Central                          | –                   | –                       | –   | –      |
| North                            | 1.67                | 0.63                    | 4.42| 0.30   |
| South                            | 0.99                | 0.47                    | 2.07| 0.98   |
| West                             | 3.21                | 0.69                    | 15.05| 0.14 |
| East                             | 2.86                | 0.32                    | 25.77| 0.35 |
| **Education**                    |                     |                         |     |
| <High school                     | –                   | –                       | –   | –      |
| High school                      | 1.28                | 0.81                    | 2.02| 0.30   |
| College degree                   | 2.09                | 1.37                    | 3.19| 0.0007 |
| Graduate                         | 3.95                | 1.27                    | 12.30| 0.018 |
| **Diagnosis date**               |                     |                         |     |
| <6 months                         | –                   | –                       | –   | –      |
| 6–12 months                      | 0.77                | 0.19                    | 3.20| 0.72   |
| 12–24 months                     | 0.58                | 0.15                    | 2.23| 0.43   |
| >24 months                       | 0.75                | 0.22                    | 2.53| 0.65   |
| **Comorbidities/medications**    |                     |                         |     |
| Diabetes mellitus                | 0.39                | 0.24                    | 0.63| 0.0002 |
| Hypertension                     | 0.60                | 0.39                    | 0.92| 0.020  |
| Thyroid disease                  | 1.18                | 0.71                    | 1.94| 0.516  |
| Coronary disease                 | 0.80                | 0.35                    | 1.81| 0.56   |
| Respiratory disease              | 0.89                | 0.48                    | 1.66| 0.71   |
| Corticosteroids                  | 4.06                | 2.53                    | 6.51| 0.0001 |
| Anti-hypertensive agents         | 0.44                | 0.22                    | 0.86| 0.0172 |
| Anti-diabetic agents             | 0.09                | 0.02                    | 0.41| 0.0017 |
| Anti-coagulants                  | 3.19                | 1.07                    | 9.58| 0.038  |
| NSAIDs                           | 5.31                | 1.20                    | 23.47| 0.0276 |
| Vitamins                         | 2.43                | 1.08                    | 5.45| 0.032  |

Significant p-values (P < 0.05) are indicated in bold.
NSAID, nonsteroidal anti-inflammatory drug.
anti-inflammatory drug, or vitamin intake had greater odds of initiating HCQ. In our study cohort, almost 11% of patients with RA/SLE in Saudi Arabia were diagnosed with COVID-19, and the incidence of COVID-19 did not differ between HCQ users (23/207 [11.11%]) and nonusers (33/304 [10.86%], Table 3). Therefore, there was no significant correlation between chronic HCQ use and COVID-19 risk among patients with RA/SLE (OR = 1.03, 95% CI = 0.58–1.81.

### Table 3. Complications of COVID-19.

| Symptom                        | Patients with COVID-19 | HCQ users | HCQ nonusers |
|--------------------------------|------------------------|-----------|--------------|
| Total                          | 56 100                 | 23 11.11  | 33 10.86     |             |
| COVID-19 symptoms              |                        |           |              |
| Asymptomatic                   | 4 7.14                 | 1 4.35    | 3 9.09       | 0.50        |
| Fatigue                        | 36 64.29               | 16 69.57  | 20 60.61     | 0.49        |
| Fever                          | 37 66.07               | 15 65.22  | 22 66.67     | 0.91        |
| Headache                       | 32 57.14               | 15 65.22  | 17 51.52     | 0.31        |
| Loss of smell and taste        | 35 62.50               | 11 47.83  | 24 72.73     | 0.62        |
| Breathing difficulty           | 17 30.36               | 7 30.43   | 10 30.30     | 0.99        |
| Dry cough                      | 22 39.29               | 6 26.09   | 16 48.48     | 0.09        |
| Diarrhea                       | 15 26.79               | 6 26.09   | 9 27.27      | 0.92        |
| Joint pain                     | 6 10.71                | 1 4.35    | 5 15.15      | 0.23        |
| Discoloration of toes          | 4 7.14                 | 2 8.70    | 2 6.06       | 0.71        |
| Symptom severity*              |                        |           |              |
| Asymptomatic                   | 5 8.93                 | 2 8.70    | 3 9.09       | –           |
| Mild/moderate                  | 39 69.64               | 17 73.91  | 22 66.67     | 0.88        |
| Severe                         | 11 19.64               | 3 13.04   | 8 24.24      | 0.61        |
| Critical                       | 1 1.79                 | 1 4.35    | 0 0          | 0.99        |
| Assigned treatment location    |                        |           |              |
| Home quarantine                | 32 57.14               | 18 78.26  | 14 42.42     | –           |
| MOH quarantine                 | 18 32.14               | 3 13.04   | 15 45.45     | 0.01        |
| Hospitalization (regular)      | 4 7.14                 | 0 0       | 4 12.12      | 0.97        |
| Hospitalization (ICU)          | 2 3.57                 | 2 8.70    | 0 0          | 0.98        |
| Hospital stay                  |                        |           |              |
| <3 days                        | 1 1.79                 | 0 0       | 1 3.03       | –           |
| 3–7 days                       | 1 1.79                 | 0 0       | 1 3.03       | –           |
| 1–2 weeks                      | 1 1.79                 | 0 0       | 1 3.03       | –           |
| >2 weeks                       | 1 1.79                 | 0 0       | 1 3.03       | –           |
| ICU stay (days)                |                        |           |              |
| <3 days                        | 1 1.79                 | 1 4.35    | 0 0          | –           |
| 3–7 days                       | 0 0                    | 0 0       | 0 0          | –           |
| 1–2 weeks                      | 1 1.79                 | 1 4.35    | 0 0          | –           |
| >2 weeks                       | 0 0                    | 0 0       | 0 0          | –           |
| <3 days                        | 0 0                    | 0 0       | 0 0          | –           |
| Oxygen therapy                 | 3 5.36                 | 0 0       | 3 9.09       | –           |
| Mechanical ventilation         | 0 0                    | 0 0       | 0 0          | –           |

*Symptom severity was based on patients’ perspectives.
COVID-19, coronavirus disease 2019; MOH, Ministry of Health; ICU, intensive care unit; HCQ, hydroxychloroquine.
The results of sensitivity analyses for disease type were similar to those of our primary analysis. There was no significant correlation between chronic HCQ use and COVID-19 risk among patients with RA (OR = 0.99, 95% CI = 0.50–1.96, \( P = 0.98 \)) or those with SLE (OR = 0.98, 95% CI = 0.43–2.19, \( P = 0.98 \)). This strengthens the robustness of our primary statistical analysis model.

The common COVID-19 symptoms in both groups were fever, dry cough, fatigue, breathing difficulty, diarrhea, headache, loss of smell or taste, toe discoloration, and joint pain. Fewer than 8% of patients with COVID-19 in our study cohort were asymptomatic (Table 3 and Figure 2). Among patients who were not chronic HCQ users, two were admitted to the intensive care unit (ICU), including one patient admitted for fewer than 3 days and one patient admitted for more than a week. No hospitalized patients who were on HCQ required oxygen therapy. Conversely, no chronic HCQ users were admitted to the ICU. However, four such patients were admitted to the hospital to receive regular care, and three received oxygen therapy. Chronic HCQ use did not decrease or prevent hospitalization or the use of oxygen therapy among patients with COVID-19.

**Discussion**

Our study explored the association between chronic HCQ use among patients with RA/SLE and the incidence of COVID-19 and its complications. The mean age of the patients in our cohort study was 44 years. As expected, more women (80%) were diagnosed with RA/SLE than men. These results agree with the results of a previous study in which 70% and 86% of the patients diagnosed with RA and SLE, respectively, were women.\(^{21}\) The main

![Figure 2. Coronavirus disease 2019 symptoms in HCQ users and nonusers. HCQ, hydroxychloroquine.](image-url)
finding of this retrospective cohort study was that there was no association between chronic HCQ use and COVID-19 risk among patients with RA/SLE.

HCQ was reported in some previous studies to be effective against multiple viruses, including SARS-CoV-2 and Middle East respiratory syndrome coronavirus. Therefore, the drug was proposed to be an option for treating COVID-19 because of the limited treatment options available at the beginning of the pandemic. Chronic HCQ use can increase the plasma levels of the drug, resulting in an adequate concentration in plasma and other tissues, including the lungs. Hence, it was proposed that chronic HCQ use could protect against COVID-19.

Gao et al. reported the efficacy of chloroquine in the treatment of COVID-19–associated pneumonia. Gautret et al. studied the effect of HCQ as a monotherapy or in combination with the macrolide antibiotic azithromycin in the treatment of COVID-19. The results revealed a reduction in the viral load following HCQ therapy, and this effect was reinforced by the addition of azithromycin. However, these findings were questionable, and the study design, outcome measure, and statistical analyses of this study were critiqued.

The serum concentration of HCQ in the study by Gautret et al. was 460 ng/mL; however, this was lower than the steady-state serum concentration of HCQ after 6 months of continuous use at a twice-daily dose of 200 mg, which resulted in a peak concentration of 1400 ng/mL. Therefore, studying the effect of chronic HCQ use on COVID-19 risk is necessarily to confirm its efficacy.

To minimize the covariates between our study groups, we only included patients with RA or SLE who visited rheumatology clinics. This strengthens our study versus other studies that compared chronic HCQ users with the general population. We collected data from 691 patients who visited rheumatology clinics in three tertiary hospitals in Riyadh, Saudi Arabia. However, because of the inefficiencies of the EHR system and the effects of the COVID-19 pandemic, which resulted in clinic closure, we contacted our patients by telephone to confirm the data collected from the EHR database and obtain detailed information about comorbidities and concurrent medications.

Our study recorded similar results regarding the effect of HCQ on COVID-19 as other studies. In an observational study, Favalli et al. observed the respiratory symptoms of COVID-19 in patients with rheumatic disease who used HCQ chronically. In another study in the United States, patients with rheumatic disease and COVID-19 had similar clinical features as patients with rheumatic disease alone, but they were more likely to require mechanical ventilation. In addition, in a large observational study in England, there was no evidence of differences in COVID-19–related mortality between chronic HCQ users and nonusers. Moreover, the current results accord with those of a recent study identifying no clinical prophylactic and therapeutic efficacy of HCQ against COVID-19 when taken at regular doses in patients with RA and SLE. In addition, another study found that the baseline consumption of HCQ did not alter the prevalence of COVID-19 in patients with RA and SLE. Furthermore, 70 HCQ chronic users died of COVID-19 in one analysis. Interestingly, the combination of HCQ and azithromycin did not improve the patients’ clinical status, but it significantly increased the risk of mortality.

Strength and limitations

Propensity score matching and inverse probability were used to adjust for differences between study groups, and several
sensitivity analyses were performed to ensure the robustness of our primary model.

This study had some limitations. There is no national database available for researchers. Instead, we used data from three tertiary hospitals in Riyadh, Saudi Arabia. The EHR system did not capture drug utilization variables, especially when patients visited different hospitals. Instead, we contacted patients to collect and verify data on the drug utilization variables. Therefore, we could not study the effects of DMARDs on COVID-19.

Conclusions

The results of this study revealed no significant association between chronic HCQ use and the incidence of COVID-19 among patients with RA/SLE. In addition, the rates of COVID-19 disease complications were similar between the two study groups. Hence, this study did not support the efficacy of HCQ in reducing the incidence or complications of COVID-19, in line with most prior research.

Acknowledgements

We acknowledge all patients who participated to the study. We also gratefully acknowledge Fadwa Salih Mahmoud and Sultan Tawfiq AlShurbaji for their assistance with data collection.

Declaration of competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and publication of this article: This research was funded by King Abdulaziz City for Science and Technology (KACST) through the fast-track funding path for Coronavirus (COVID-19) (grant number 5-20-01-016-0002; PI. IAW).

Author contributions

IAW, HA, and HAA participated in the design of the study. IAW, HA, HAA, SAA, AMA, NSA, MAA, HMA, AHA, FA, and MAH prepared the methodology. IAW, ASA, NSA, MAA, HMA, AHA, and MAH supervised the project. IAW, HAA, and HA wrote the original draft. DSA, AAS, OSA, and RKA collected data. SAA, AMA, DSA, AAS, ASA, and FA reviewed and edited the writing. HA and IAW conducted the formal analysis. HA performed the statistical analysis. All authors reviewed and approved the final manuscript.

ORCID iD

Hussain Alqhtani https://orcid.org/0000-0002-1840-4519

References

1. Tregoning JS, Flight KE, Higham SL, et al. Progress of the COVID-19 vaccine effort: viruses, vaccines and variants versus efficacy, effectiveness and escape. Nat Rev Immunol 2021; 21: 626–636.
2. Alexander SP, Armstrong JF, Davenport AP, et al. A rational roadmap for SARS-CoV-2/COVID-19 pharmacotherapeutic research and development: IUPHAR review 29. British journal of pharmacology 2020; 177: 4942–4966.
3. Esposito S, Noviello S and Pagliano P. Update on treatment of COVID-19: ongoing studies between promising and disappointing results. Infez Med 2020; 28: 198–211.
4. Jirjees F, Saad AK, Al Hano Z, et al. COVID-19 Treatment Guidelines: Do They Really Reflect Best Medical Practices to Manage the Pandemic? Infect Dis Rep 2021; 13: 259–284.
5. Lee Z, Rayner CR, Forrest JJ, et al. The rise and fall of hydroxychloroquine for the treatment and prevention of COVID-19. Am J Trop Med Hyg 2021; 104: 35.
6. Barros Edington FL, De Rezende DF, Dos Santos LF, et al. Efficacy of hydroxychloroquine in the prevention of thromboembolic events: A systematic review and meta-analysis. *Lupus* 2022; 31: 238–245.

7. Deng J, Zhou F, Heybati K, et al. Efficacy of chloroquine and hydroxychloroquine for the treatment of hospitalized COVID-19 patients: a meta-analysis. *Future Virol.* 2022; 17(2): 95–118.

8. Pileggi GS, Ferreira GA, Gomides Reis AP, et al. Chronic use of hydroxychloroquine did not protect against COVID-19 in a large cohort of patients with rheumatic diseases in Brazil. *Adv Rheumatol* 2021; 61: 61.

9. Trefond L, Drumez E, Andre M, et al. Impact of hydroxychloroquine used as DMARD on SARS CoV-2 tests and infection evolution in a population of 871 patients with inflammatory rheumatic and musculoskeletal diseases. *Joint Bone Spine* 2021; 88: 105226–105226.

10. Jung SY, Kim MS, Kim MC, et al. Effect of hydroxychloroquine pre-exposure on infection with SARS-CoV-2 in rheumatic disease patients: a population-based cohort study. *Clin Microbiol Infect* 2021; 88: 105226–105226.

11. Rainsford KD, Parke AL, Clifford-Rashotte M, et al. Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases. *Inflammopharmacology* 2015; 23: 231–269.

12. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis* 2020; 71: 732–739.

13. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov* 2020; 6: 1–4.

14. Fantini J, Di Scala C, Chahinian H, et al. Structural and molecular modelling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection. *Int J Antimicrob Agents* 2020; 55: 105960.

15. Fantini J, Chahinian H and Yahi N. Synergistic antiviral effect of hydroxychloroquine and azithromycin in combination against SARS-CoV-2: What molecular dynamics studies of virus-host interactions reveal. *Int J Antimicrob Agents* 2020; 55: 106007.

16. Derendorf H. Excessive lysosomal ion-trapping of hydroxychloroquine and azithromycin. *Int J Antimicrob Agents* 2020; 55: 106007.

17. Schrezenmeier E and Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nat Rev Rheumatol* 2020; 16: 155–166.

18. United States Food and Drug Administration. Coronavirus (COVID-19) Update: Daily Roundup, www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-march-30-2020 (30 March 2020) USFDA Coronavirus (COVID-19) Update Daily Roundup March 30. Internet: FDA 2020.

19. United States Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine. www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and (15 Jun 2020)

20. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; 147: 573–577.

21. Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. *Semin Arthritis Rheum* 1993; 23: 82–91.

22. Savarino A, Di Trani L, Donatelli I, et al. New insights into the antiviral effects of chloroquine. *Lancet Infect Dis* 2006; 6: 67–69.

23. Dyall J, Gross R, Kindrachuk J, et al. Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome: Current Therapeutic Options and Potential Targets for Novel Therapies. *Drugs* 2017; 77: 1935–1966.
24. Li X, Wang Y, Agostinis P, et al. Is hydroxychloroquine beneficial for COVID-19 patients? Cell Death Dis 2020; 11: 512.

25. Ferreira A, Oliveira ESA and Bettencourt P. Chronic treatment with hydroxychloroquine and SARS-CoV-2 infection. J Med Virol 2021; 93: 755–759.

26. Gao J, Tian Z and Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020; 14: 72–73.

27. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020; 56: 105949.

28. Machiels JD, Bleeker-Rovers CP, Ter Heine R, et al. Reply to Gautret et al: hydroxychloroquine sulfate and azithromycin for COVID-19: what is the evidence and what are the risks? Int J Antimicrob Agents 2020; 56: 106056.

29. Al-Rawi H, Meggitt SJ, Williams FM, et al. Steady-state pharmacokinetics of hydroxychloroquine in patients with cutaneous lupus erythematosus. Lupus 2018; 27: 847–852.

30. Favalli EG, Monti S, Ingegnoli F, et al. Incidence of COVID-19 in Patients With Rheumatic Diseases Treated With Targeted Immunosuppressive Drugs: What Can We Learn From Observational Data? Arthritis Rheumatol 2020; 72: 1600–1606.

31. D'Silva KM, Serling-Boyd N, Wallwork R, et al. Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US ‘hot spot’. Ann Rheum Dis 2020; 79: 1156–1162.

32. Mollaeian A, Kim DS and Haas CJ. COVID-19 Prevalence and Outcomes among Individuals with Rheumatoid Arthritis and Systemic Lupus Erythematosus Taking Hydroxychloroquine: A Retrospective Analysis. Open Rheumatol J 2021; 15: 69–76.

33. Rentsch CT, DeVito NJ, MacKenna B, et al. Effect of pre-exposure use of hydroxychloroquine on COVID-19 mortality: a population-based cohort study in patients with rheumatoid arthritis or systemic lupus erythematosus using the Open SAFELY platform. Lancet Rheumatol 2021; 3: e19–e27.

34. Fiolet T, Guihur A, Rebeaud ME, et al. Effect of hydroxychloroquine with or without azithromycin on the mortality of coronavirus disease 2019 (COVID-19) patients: a systematic review and meta-analysis. Clin Microbiol Infect 2021; 27: 19–27.