

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

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## 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

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## 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.<sup>1</sup> 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.<sup>2</sup> In early 2020, hundreds of drugs were trialed in mostly hospitalized patients with COVID-19, generating a massive amount of data of varying quality.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5</sup> Some studies revealed its effectiveness in preventing thromboembolic events.<sup>6</sup>

Conversely, several previous studies, as reviewed in a recent review,<sup>7</sup> revealed inconsistent anti-COVID-19 effects of HCQ, and no convincing efficacy was recorded in the majority of retrospective and observational trials.<sup>8–10</sup>

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.<sup>11</sup> 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.<sup>12</sup> 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.<sup>13</sup> A ganglioside-binding domain is found at the N-terminus of S protein.<sup>14</sup> 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.<sup>15</sup> 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.<sup>16</sup> 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- $\alpha$  and TLR signaling.<sup>17</sup> 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.<sup>18</sup> 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.<sup>19</sup> HCQ was initially proposed to represent an effective, safe, and affordable drug to control the COVID-19 pandemic globally.<sup>13</sup> 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.<sup>20</sup>

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 sub-groups, 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 consecutive prescriptions during the last 6 months. The primary outcome was a positive COVID-19 test from March 2020 to February 2021. Data on COVID-19 were collected by asking the patients if they had

been diagnosed with COVID-19 and confirmed using data from the National Health Laboratory at the Saudi Ministry of Health.

### **Inclusion and exclusion criteria**

Patients aged  $\geq 18$  years with a diagnosis of RA/SLE were included. 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  $\pm$  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

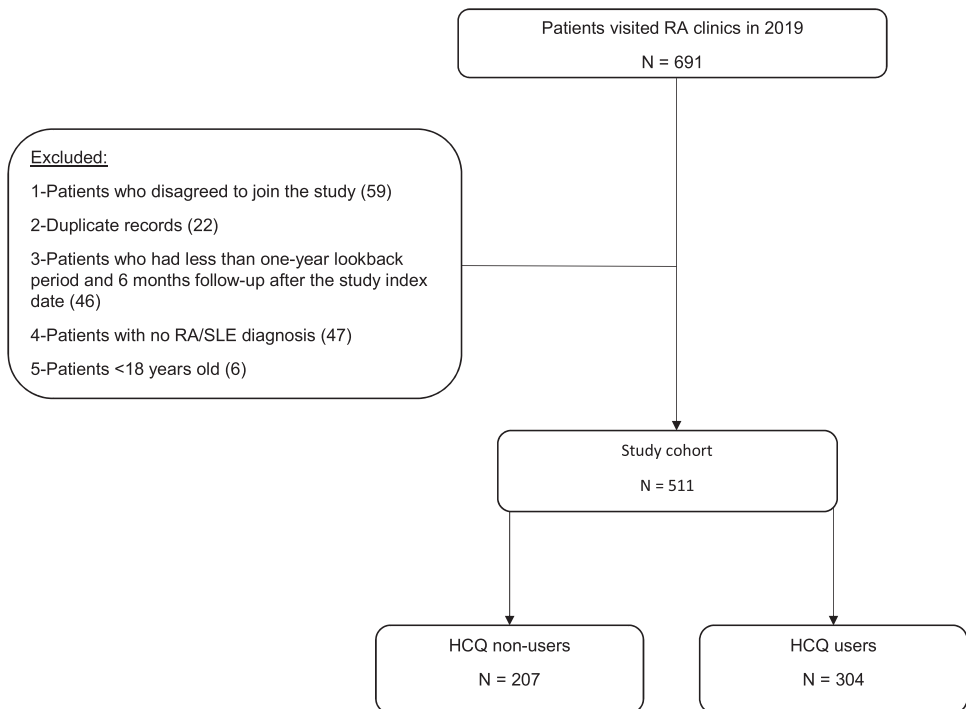
level of 0.05 and performed using SAS version 9.4 (SAS Institute Inc., version 9.4, Cary, NC, USA).

## 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.



**Figure 1.** Study flowchart.

**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	<b>86.51</b>
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	<b>22.71</b>	31	10.20
Hypertension	105	20.55	53	<b>25.60</b>	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	<b>36.84</b>
Anti-hypertensive agents	37	7.24	22	<b>10.63</b>	15	4.93
Anti-diabetic agents	16	3.13	14	<b>6.76</b>	2	0.66
Anti-coagulants	22	4.31	4	1.93	18	<b>5.92</b>
NSAIDs	17	3.33	2	0.97	15	<b>4.93</b>
Vitamins	35	6.85	8	3.86	27	<b>8.88</b>

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.

**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
<i>Demographics</i>				
Age	0.976	0.96	0.99	<b>0.0005</b>
<i>Sex</i>				
Male	–	–	–	–
Female	2.10	1.33	3.31	<b>0.0015</b>
<i>Region</i>				
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
<i>Education</i>				
<High school	–	–	–	–
High school	1.28	0.81	2.02	0.30
College degree	2.09	1.37	3.19	<b>0.0007</b>
Graduate	3.95	1.27	12.30	<b>0.018</b>
<i>Diagnosis date</i>				
<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
<i>Comorbidities/medications</i>				
Diabetes mellitus	0.39	0.24	0.63	<b>0.0002</b>
Hypertension	0.60	0.39	0.92	<b>0.020</b>
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	<b>0.0001</b>
Anti-hypertensive agents	0.44	0.22	0.86	<b>0.0172</b>
Anti-diabetic agents	0.09	0.02	0.41	<b>0.0017</b>
Anti-coagulants	3.19	1.07	9.58	<b>0.038</b>
NSAIDs	5.31	1.20	23.47	<b>0.0276</b>
Vitamins	2.43	1.08	5.45	<b>0.032</b>

Significant p-values ( $P < 0.05$ ) are indicated in bold.

NSAID, nonsteroidal anti-inflammatory drug.

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, 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.

	Patients with COVID-19		HCQ users		HCQ nonusers		P
	N	%	N	%	N	%	
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.



$P=0.93$ ). 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.

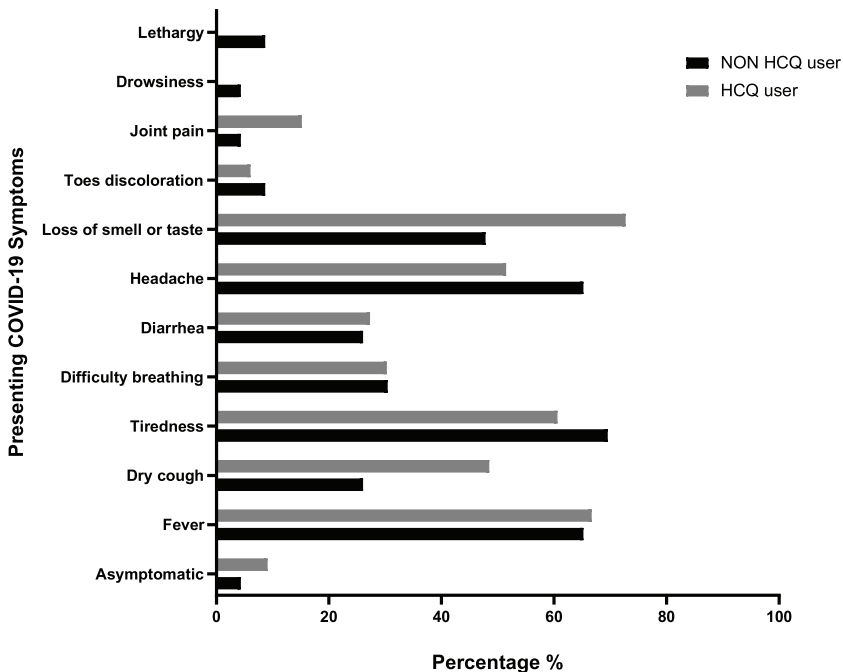
The common COVID-19 symptoms in both groups were fever, dry cough, fatigue, breathing difficulty, diarrhea, headache, loss of smell or taste, toe discoloration, and joint pain. Fewer than 8% of patients with COVID-19 in our study cohort were asymptomatic (Table 3 and Figure 2).

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.<sup>21</sup> The main



**Figure 2.** Coronavirus disease 2019 symptoms in HCQ users and nonusers. HCQ, hydroxychloroquine.

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.<sup>22,23</sup> 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.<sup>24</sup> 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.<sup>25</sup>

Gao *et al.* reported the efficacy of chloroquine in the treatment of COVID-19-associated pneumonia.<sup>26</sup> 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.<sup>27</sup> However, these findings were questionable, and the study design, outcome measure, and statistical analyses of this study were critiqued.<sup>28</sup>

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.<sup>27,29</sup> 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.<sup>30</sup> 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.<sup>31</sup> 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.<sup>32</sup> Furthermore, 70 HCQ chronic users died of COVID-19 in one analysis.<sup>33</sup> Interestingly, the combination of HCQ and azithromycin did not improve the patients' clinical status, but it significantly increased the risk of mortality.<sup>34</sup>

## 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.

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## 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.

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## 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.

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