Baseline use of hydroxychloroquine or immunosuppressive drugs and the risk of coronavirus disease 2019

Ji-Won Kim¹, Sang Gyu Kwak², Hwajeong Lee³, Seong-Kyu Kim¹, Jung-Yoon Choe³, and Sung-Hoon Park¹

¹Division of Rheumatology, Department of Internal Medicine, ²Department of Medical Statistics, Daegu Catholic University School of Medicine, Daegu, Korea

Baseline use of hydroxychloroquine or immunosuppressive drugs and the risk of coronavirus disease 2019

Patients
South Korea National Health Insurance Sharing-COVID-19 Database (n = 129,120)

Outcome
COVID-19 infection

Results

|                | COVID-19 incidence (%) | Odds ratio (95% CI) |
|----------------|------------------------|---------------------|
| HCQ use (-)    | 6.8%                   | 1 (reference)       |
| HCQ use (+)    | 7.1%                   | 1.05 (0.58-1.89)    |

No difference in COVID-19 prevention

Conclusion
The risk of COVID-19 did not differ between HCQ users and non-users.
INTRODUCTION

No specific drug is currently available for the treatment and prevention of coronavirus disease 2019 (COVID-19). As an alternative, several available drugs, including hydroxychloroquine (HCQ), have gained attention in the treatment of COVID-19. After the finding that HCQ inhibited the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro [1], early clinical studies indicated that HCQ treatment could reduce the time to clinical recovery and promote more frequent viral clearance compared with routine treatment [2,3].

Long-term usage of HCQ is common in patients with rheumatic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Whether HCQ has a preventive effect on COVID-19 in patients with rheumatic diseases is not clear. The incidence and outcomes of COVID-19 in patients with rheumatic diseases might also be affected by the use of glucocorticoids and other immunosuppressive drugs. A recent analysis of data from a global registry of patients with rheumatic diseases diagnosed with COVID-19 indicated that the use of moderate- to high-dose glucocorticoids, but not biologics or antimalarials, was associated with increased risk of hospitalization for COVID-19 [4]. Chronic HCQ use did not prevent COVID-19 in earlier case series or small-sized cohort studies [5-8], but a beneficial effect of HCQ in COVID-19 prevention was identified in a retrospective study based on a national healthcare database [9]. In a recent placebo-controlled clinical trial regarding HCQ in postexposure prophylaxis, there was no difference in incident COVID-19 between HCQ and the placebo [10]. However, the data concerning the role of HCQ in COVID-19 prevention are still lacking.

Therefore, we aimed to investigate whether HCQ can prevent COVID-19 by analyzing cases in a national healthcare database. We also investigated the effect of other disease-modifying antirheumatic drugs (DMARDs), and biological DMARDs other than abatacept did not increase the risk of COVID-19.

METHODS

Database

This study is based on the South Korea National Health Insurance Sharing (NHIS)-COVID-19 database, which contains all individuals who received swab tests for COVID-19 between...
January 2020 and May 2020. Claims data of this group between January 1, 2015 and May 31, 2020 are integrated in this database. COVID-19 diagnosis was defined as a positive polymerase chain reaction for SARS-CoV-2 RNA from nasopharyngeal and oropharyngeal swabs. The COVID-19 negative control group (SARS-CoV-2 negative) includes all individuals who were tested for COVID-19 by nasopharyngeal and oropharyngeal swab tests but were not diagnosed with COVID-19. COVID-19 swab tests were performed for suspicion of COVID-19 or after contact with COVID-19 patients. The study protocol was approved by the Institutional Review Board of Daegu Catholic University Medical Center (CR-20-073). Informed consent was waived because the database is anonymized.

**Study design and outcome measures**
The primary outcome was the comparative risk of COVID-19 between HCQ users and non-users. Using a cross-sectional design, all individuals in the NHIS-COVID-19 database were classified into HCQ users and non-users based on their use of HCQ within 3 months of the examination date for COVID-19. The secondary outcome was the effect of DMARDs and immunosuppressive drugs on the incidence of COVID-19. Using a case-control study design, factors associated with COVID-19 in subpopulations of patients with RA or SLE were investigated.

**Variables**
Age, sex, rheumatologic diagnosis, comorbidities, and medications were obtained from the NHIS-COVID-19 database. Age on the date of COVID-19 testing and sex were recorded. Rheumatologic diagnoses were identified by diagnostic codes (International Classification of Diseases, 10th edition [ICD-10]) in the claims data from January 1, 2015, to the test date, and included RA, SLE, ankylosing spondylitis, Sjögren’s syndrome, and systemic sclerosis (ICD-10 codes M05, M32, M45, M35, and M34). The presence of comorbidities was also determined by the presence of corresponding ICD-10 diagnostic codes from January 1, 2015 to the examination date, and the comorbidities included diabetes mellitus, hypertension, cardiovascular disease (ischemic heart disease, congestive heart failure, cerebrovascular accident, and peripheral vascular disease), chronic lung disease (asthma, chronic obstructive pulmonary disease, and interstitial lung disease), and chronic kidney disease. Use of medications including glucocorticoids (and its daily dosage), HCQ, methotrexate, sulfasalazine, leflunomide, tacrolimus, tumor necrosis factor α (TNF-α) inhibitors, tocilizumab, abatacept, rituximab, and tofacitinib within 3 months of the examination date was obtained from the database.

**Statistical analysis**
All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA). Characteristics of all study participants stratified by HCQ use were compared by chi-square test. A 1:1 propensity score matching was performed to balance the characteristics of HCQ users and non-users using the nearest neighbor method with a 0.2 caliper. Odds ratio (OR) and 95% confidence interval (CI) for COVID-19 with HCQ use were determined in the propensity score-matched population. Next, among patients with RA or SLE, characteristics of COVID-19 patients and negative controls were compared using chi-square test or Fisher’s exact test. Factors associated with COVID-19 were examined using binary logistic regression analysis. Variables with p values < 0.2 in simple logistic regression, along with age and sex, were included in the multiple logistic regression. p values < 0.05 were considered statistically significant.

**RESULTS**

**Study population**
There were 8,070 people with COVID-19 (SARS-CoV-2 positive) and 121,050 negative controls (SARS-CoV-2 negative) included from the NHIS-COVID-19 database. Among all 129,120 participants, there were 381 HCQ users. Characteristics of HCQ users and non-users are described in Table 1. HCQ users were older than non-users and more women were found among HCQ users. Rheumatic diseases including RA, SLE, ankylosing spondylitis, Sjögren’s syndrome, and systemic sclerosis were more common in HCQ users, and comorbidities including hypertension, cardiovascular disease, chronic lung disease, and chronic kidney disease tended to appear more frequently in HCQ users, although statistical significance was not found.

**Risk of COVID-19 according to HCQ use**
HCQ users and non-users were matched 1:1 to balance their characteristics (Table 1). Age, sex, rheumatic diseases, comorbidities, and medications except glucocorticoids and methotrexate were similar between HCQ users and non-us-
ers after propensity score matching. In the matched population, 24 of 340 HCQ users (7.1%) had COVID-19 diagnoses and 23 of 340 non-users (6.8%) had COVID-19 diagnoses, indicating a similar risk of COVID-19 between HCQ users and non-users (OR, 1.05; 95% CI, 0.58 to 1.89; \( p = 0.880 \)) (Table 2).

Table 1. Characteristics of study participants before and after propensity score matching

| Variable                        | Before propensity score matching | After propensity score matching\(^a\) |
|---------------------------------|----------------------------------|-------------------------------------|
|                                 | HCQ use (n = 381) | No HCQ use (n = 128,739) | \( p \) value | HCQ use (n = 340) | No HCQ use (n = 340) | \( p \) value |
| Age, yr\(^b\)                   |                      |                              |                |                      |                              |            |
| < 40                            | 38 (10.0)            | 51,898 (40.3)                | < 0.001        | 31 (9.1)            | 30 (8.8)                  | 0.971       |
| 40–60                           | 158 (41.5)           | 41,490 (32.2)                |                | 152 (44.7)          | 150 (44.1)                |            |
| ≥ 60                            | 185 (48.6)           | 35,351 (27.5)                |                | 157 (46.2)          | 160 (47.1)                |            |
| Female sex\(^b\)                | 327 (85.8)           | 77,017 (59.8)                | < 0.001        | 297 (87.4)          | 298 (87.7)                | 0.908       |
| Rheumatologic diagnosis\(^c\)  |                      |                              |                |                      |                              |            |
| Rheumatoid arthritis            | 256 (67.2)           | 255 (0.2)                    | < 0.001        | 224 (65.9)          | 224 (65.9)                | 1.000       |
| Systemic lupus erythematosus    | 74 (19.4)            | 209 (0.2)                    | < 0.001        | 59 (17.4)           | 59 (17.4)                 | 1.000       |
| Ankylosing spondylitis          | 3 (0.8)              | 191 (0.2)                    | 0.001          | 3 (0.9)             | 6 (1.8)                   | 0.314       |
| Sjögren's syndrome              | 73 (19.2)            | 298 (0.2)                    | < 0.001        | 63 (18.5)           | 63 (18.5)                 | 1.000       |
| Systemic sclerosis              | 6 (1.6)              | 18 (0.0)                     | < 0.001        | 4 (1.2)             | 4 (1.2)                   | 1.000       |
| Comorbidities\(^c\)            |                      |                              |                |                      |                              |            |
| Diabetes mellitus               | 9 (2.4)              | 4,921 (3.9)                  | 0.128          | 7 (2.1)             | 8 (2.4)                   | 0.794       |
| Hypertension                    | 12 (3.2)             | 2,311 (1.8)                  | 0.052          | 7 (2.1)             | 7 (2.1)                   | 1.000       |
| Cardiovascular disease          | 14 (3.7)             | 3,596 (2.8)                  | 0.319          | 9 (2.7)             | 8 (2.4)                   | 0.806       |
| Chronic lung disease            | 6 (1.6)              | 1,140 (0.9)                  | 0.161          | 3 (0.9)             | 6 (1.8)                   | 0.314       |
| Chronic kidney disease          | 3 (0.8)              | 379 (0.3)                    | 0.081          | 0                   | 0                         | 1.000       |
| Current medications\(^d\)      |                      |                              |                |                      |                              |            |
| Glucocorticoid                  | 295 (77.4)           | 436 (0.3)                    | < 0.001        | 261 (76.8)          | 197 (57.9)                | < 0.001     |
| Glucocorticoid dose ≥ 10 mg/day | 170 (44.6)           | 289 (0.2)                    | < 0.001        | 146 (42.9)          | 120 (35.3)                | 0.041       |
| Methotrexate                    | 203 (53.3)           | 167 (0.1)                    | < 0.001        | 186 (54.7)          | 123 (36.2)                | < 0.001     |
| Leflunomide                     | 64 (16.8)            | 69 (0.1)                     | < 0.001        | 58 (17.1)           | 60 (17.7)                 | 0.840       |
| Tacrolimus                      | 33 (8.7)             | 30 (0.0)                     | < 0.001        | 31 (9.1)            | 24 (7.1)                  | 0.325       |
| TNF-α inhibitors                | 12 (3.2)             | 29 (0.0)                     | < 0.001        | 11 (3.2)            | 8 (2.4)                   | 0.485       |
| Tocilizumab                     | 5 (1.3)              | 6 (0.0)                      | < 0.001        | 5 (1.5)             | 5 (1.5)                   | 1.000       |
| Abatacept                        | 3 (0.8)              | 5 (0.0)                      | < 0.001        | 3 (0.9)             | 5 (1.5)                   | 0.477       |
| Rituximab                       | 1 (0.3)              | 1 (0.0)                      | < 0.001        | 1 (0.3)             | 1 (0.3)                   | 1.000       |
| Tofacitinib                     | 1 (0.3)              | 1 (0.0)                      | < 0.001        | 1 (0.3)             | 1 (0.3)                   | 1.000       |

Values are presented as number (%).

HCQ, hydroxychloroquine; TNF, tumor necrosis factor.

\(^a\)Age, sex, rheumatologic diagnosis, and comorbidities were matched in the propensity score matching analysis.

\(^b\)As recorded on the date of COVID-19 testing.

\(^c\)Information on rheumatologic diagnoses and comorbidities is based on diagnostic codes (International Classification of Diseases, 10th edition [ICD-10]) in the claims data from January 1, 2015, to the test date.

\(^d\)Use of medications within 3 months of the examination date was obtained from the database.
Factors associated with COVID-19 in patients with RA

Total 511 patients with RA were included in the database. Among the RA patients, 33 were diagnosed with COVID-19 and 478 were not. Characteristics of these patients are described in Supplementary Table 1. Age and sex were similar between COVID-19 patients and negative controls. Chronic lung disease was significantly more frequent in RA patients diagnosed with COVID-19 than in those who were not. Use of glucocorticoids, HCQ, methotrexate, sulfasalazine, leflunomide, and tacrolimus did not differ significantly between those diagnosed with COVID-19 or not. Use of abatacept was more common in RA patients diagnosed with COVID-19, while other biological or targeted synthetic DMARDs such as TNF-α inhibitors, tocilizumab, rituximab, and tofacitinib did not differ.

Multiple logistic regression analysis showed that chronic lung disease was associated with incident COVID-19 (adjusted OR, 6.07; 95% CI, 1.10 to 33.59; \( p = 0.039 \)) after adjusting for age, sex, HCQ, sulfasalazine, and abatacept use (Supplementary Table 2). HCQ use was not associated with incident COVID-19 (adjusted OR, 1.51; 95% CI, 0.69 to 3.32; \( p = 0.304 \)). Patients treated with abatacept were more likely to have COVID-19 (adjusted OR, 5.49; 95% CI, 1.02 to 29.66; \( p = 0.048 \)) after adjusting for age, sex, HCQ, sulfasalazine, and chronic lung disease. However, the statistical significance of abatacept use disappeared when adjusted for HCQ, sulfasalazine, and chronic lung disease (adjusted OR, 5.20; 95% CI, 0.97 to 27.77; \( p = 0.054 \)).

Factors associated with COVID-19 in patients with SLE

Total 283 patients with SLE were included in the database. Among the SLE patients, 20 were diagnosed with COVID-19 and 263 were not. Age, sex, comorbidities, and medications including HCQ did not differ between SLE patients with and without COVID-19 diagnosis (Supplementary Table 3). One patient (5.0%) in the COVID-19 group and two patients (0.8%) in the negative control group had chronic lung disease. In the multiple logistic regression analysis, chronic lung disease tended to be associated with incident COVID-19 (adjusted OR, 10.70; 95% CI, 0.78 to 146.03; \( p = 0.076 \)) after adjusting for age and sex (Supplementary Table 4).

DISCUSSION

This nationwide retrospective study clarifies the association between HCQ use and COVID-19 diagnosis. The risk of COVID-19 did not differ between HCQ users and non-users after controlling for confounding variables. We also examined the factors associated with COVID-19 in patients with RA or SLE. There was no association between COVID-19 and use of either glucocorticoids or conventional DMARDs, including HCQ. No biological DMARD other than abatacept was associated with COVID-19. However, underlying chronic lung disease was associated with increased risk of COVID-19.

The finding that HCQ does not have a preventive role in COVID-19 seems to parallel the results of recent large-scale clinical studies showing no effect of HCQ in the treatment of COVID-19 [11-13]. HCQ administration did not reduce the risk of admission to the intensive care unit, intubation, or death in hospitalized patients with COVID-19 [11,12], and a randomized controlled trial showed no benefit of HCQ administration for negative conversion of SARS-CoV-2 compared with standard care alone in patients with mild to moderate COVID-19 [13]. These populations received HCQ at a daily dose of 400 to 800 mg with or without a loading dose of 1200 mg, which was sufficient to inhibit SARS-CoV-2 infection in a simulation [1]. Most of the patients were treated with HCQ within 48 hours of presentation to the hospital in the aforementioned studies [11,12]. This is an important point because earlier treatment in COVID-19 might be more effective than later treatment, as suggest-

---

Table 2. Effect of HCQ on COVID-19 risk in the propensity score-matched population

| Variable   | No. of patients with COVID-19 | COVID-19 incidence rate, % | OR (95% CI)       | \( p \) value |
|------------|-------------------------------|----------------------------|-------------------|--------------|
| HCQ use    | 24                            | 7.1                        | 1.05 (0.58–1.89)  | 0.880        |
| No HCQ use | 23                            | 6.8                        | Reference         |              |

The propensity score-matched population included 340 HCQ users and 340 non-users. HCQ, hydroxychloroquine; COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval.
ed by a post-hoc subgroup analysis in a randomized trial of lopinavir-ritonavir treatment for COVID-19 [14]. HCQ treatment in patients with COVID-19 may show no therapeutic benefit despite optimal dosing regimen and timing of treatment initiation.

The question remains whether HCQ can prevent symptomatic infection before COVID-19 has fully developed in at-risk individuals. Given that prophylactic administration had potent antiviral activity against SARS-CoV in vivo and that the therapeutic antiviral activity is dependent on the time to drug initiation after infection [15], HCQ might have preventive role when it is administered as early as possible. The incidence of COVID-19 did not differ between individuals in a randomized placebo-controlled trial who received HCQ or placebo within 4 days after high- or moderate-risk exposure to confirmed COVID-19 patients [10], and clinical trials of HCQ for preexposure prophylaxis in COVID-19 (e.g., the Healthcare Worker Exposure Response and Outcomes of HCQ [HERO-HCQ] trial) are still ongoing. Although our study did not include information about SARS-CoV-2 exposure, HCQ users were taking HCQ prior to the examination date, thus enabling the assessment of the potential prophylactic efficacy of HCQ in COVID-19. Consistent with our study, in a recent retrospective analysis of another large healthcare database, chronic use of HCQ prior to SARS-CoV-2 testing did not appear to prevent COVID-19 [16].

Understanding the effect of immunosuppressive drugs on the risk and course of COVID-19 will guide clinicians in the treatment of patients with immune-mediated inflammatory diseases [17,18]. Several studies have examined the association between immunosuppressive drugs and hospitalization in COVID-19. Two cohort studies, one with 86 COVID-19 patients with immune-mediated inflammatory diseases and the other with 600 COVID-19 patients with rheumatic diseases, found that use of glucocorticoids, particularly at higher doses, was associated with increased risk of hospitalization [4,19]. Other immunosuppressive drugs do not seem to increase the hospitalization risk and severity of COVID-19, although data are conflicting [4,8,19-21]. Use of conventional DMARDs was not associated with hospitalization risk in the cohort of 600 patients with rheumatic diseases, whereas previous use of methotrexate was associated with an increased risk of hospitalization in the cohort of 86 patients with inflammatory diseases. On the other hand, patients with rheumatic diseases who use biological DMARDs, particularly TNF-α inhibitors, had reduced hospitalization risk [4,19,21]. This might be supported by the observation of higher levels of the cytokines TNF-α and interleukin 6 in severe COVID-19 cases [22,23]. Our study examined the association between immunosuppressive drugs and the incidence of COVID-19. Among 18 patients treated with TNF-α inhibitors and 11 patients treated with tocilizumab, none was diagnosed with COVID-19. Previous use of abatacept was more common in patients with COVID-19 in this study. However, a larger study would be needed to confirm the correlation between abatacept use and COVID-19. The incidence of COVID-19 among large numbers of patients with rheumatic diseases treated with biological or targeted synthetic DMARDs was not different from that of general population [24,25]. Thus, there is so far no convincing evidence that immunosuppressive drugs increase the risk of COVID-19. We might not need to withdraw these drugs if there is no evidence of COVID-19. Cessation of these drugs might lead to disease flare or relapse, which can be followed by dose escalation of steroids, possibly with an unfavorable effect on the risk or course of COVID-19. Therefore, for patients with rheumatic diseases, continuation of their usual treatments will be of greater benefit through prevention of disease flares during the COVID-19 pandemic.

Comorbidities increase the risk of critical illness and death in patients with SARS-CoV-2 infection. Chronic lung disease, hypertension, diabetes, cardiovascular disease, and chronic kidney disease are known to increase the risk of hospitalization, acute respiratory distress syndrome, or death [23,26-29]. The impact of comorbidities on the incidence of SARS-CoV-2 infection is still not fully known. Our subgroup analysis of RA patients with and without SARS-CoV-2 infection identified chronic lung disease as an independent risk factor for SARS-CoV-2 infection. Airway disease and interstitial lung disease are not uncommon in patients with RA [30], and rheumatologists must be aware of the high susceptibility of these patients to SARS-CoV-2 infection.

There are several limitations in the study. First, adherence to HCQ or blood concentration of HCQ were not investigated. It is unclear whether the HCQ users had optimal blood concentrations of HCQ. A suboptimal blood concentration of HCQ might be associated with low prophylactic efficacy for COVID-19, as with the HCQ concentration-response relationship in rheumatic diseases [31,32]. Second, because this retrospective study was based on the claims database, medical chart review was not possible, and other factors,
such as disease activity of rheumatic diseases, could not be considered. Moreover, diagnoses of rheumatic diseases and comorbidities were determined by ICD diagnostic codes without clinical information. Third, the extent of virus exposure could not be determined in this study. Healthy volunteers who were exposed to higher doses of influenza virus experienced more severe disease [33], but the relationship between initial SARS-CoV-2 dose and disease severity is unknown. One study has shown higher viral load in severe disease [34], whereas another found no relation between viral load and disease severity [35]. Either way, the amount of virus is only one factor in establishing infection. Other factors, such as host responses to the virus, may also be critical.

In conclusion, HCQ use did not prevent SARS-CoV-2 infection in a retrospective analysis of national population-based real-world data. Other immunosuppressive drugs including glucocorticoids and conventional and biological DMARDs did not increase the incidence of SARS-CoV-2 infection, although the correlation between abatacept use and COVID-19 incidence needs to be confirmed in further studies. Unlike these medications, comorbidities, specifically chronic lung disease, do affect the COVID-19 risk in RA patients.

KEY MESSAGE

1. The risk of coronavirus disease 2019 (COVID-19) did not differ between hydroxychloroquine users and non-users.
2. Use of glucocorticoids, conventional disease-modifying antirheumatic drugs (DMARDs), and biological DMARDs other than abatacept did not increase the risk of COVID-19.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

This study was supported by a research grant from Daegu Medical Association COVID-19 scientific committee (received by Sung-Hoon Park) and a grant from the National Research Foundation of Korea (NRF) funded by the Korea government (MSIT) (No. NRF-2019R1G1A1100421, received by Ji-Won Kim).

REFERENCES

1. 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.
2. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv 2020 Apr 10. https://doi.org/10.1101/2020.03.22.20040758.
3. 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.
4. Gianfrancesco M, Hyrich KL, Al-Adely S, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2020;79:859-866.
5. Mathian A, Mahevas M, Rohmer J, et al. Clinical course of coronavirus disease 2019 (COVID-19) in a series of 17 patients with systemic lupus erythematosus under long-term treatment with hydroxychloroquine. Ann Rheum Dis 2020;79:837-839.
6. König MF, Kim AH, Scheetz MH, et al. Baseline use of hydroxychloroquine in systemic lupus erythematosus does not preclude SARS-CoV-2 infection and severe COVID-19. Ann Rheum Dis 2020;79:1386-1388.
7. Bozzaalla Cassione E, Zanframundo G, Biglia A, Codullo V, Montecucco C, Cavagna L. COVID-19 infection in a northern-Italian cohort of systemic lupus erythematosus assessed by telemedicine. Ann Rheum Dis 2020;79:1382-1383.
8. Gendebien Z, von Frenckell C, Ribbens C, et al. Systematic analysis of COVID-19 infection and symptoms in a systemic lupus erythematosus population: correlation with disease characteristics, hydroxychloroquine use and immunosuppressive treatments. Ann Rheum Dis 2021;80:218244.
9. Ferreira A, Oliveira-E-Silva A, Bettencourt P. Chronic treatment with hydroxychloroquine and SARS-CoV-2 infection. J Med Virol 2021;93:755-759.
10. Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for COVID-19. N Engl J Med 2020;383:517-525.
11. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med 2020;382:2441-2448.
12. Mahevas M, Tran VT, Roumier M, et al. Clinical efficacy of hydroxychloroquine in patients with COVID-19 pneumonia who require oxygen: observational comparative study using routine care data. BMJ 2020;369:m1844.
13. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ 2020;369:m1849.
14. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. N Engl J Med. 2020;382:1787-1799.
15. Sheahan TP, Sims AC, Zhou S, et al. An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. Sci Transl Med 2020;12:eabb5883.
16. Gendelman O, Amital H, Bragazzi NL, Watad A, Chodick G. Continuous hydroxychloroquine or colchicine therapy does not prevent infection with SARS-CoV-2: insights from a large healthcare database analysis. Autoimmun Rev 2020;19:102566.
17. Seo MR, Kim JW, Park EJ, et al. Recommendations for the management of patients with systemic rheumatic diseases during the coronavirus disease pandemic. Korean J Intern Med 2020;35:1317-1332.
18. Seo MR, Kim JW, Park EJ, et al. Recommendations for the management of patients with systemic rheumatic diseases during the coronavirus disease pandemic. J Rheum Dis 2020;27:218-232.
19. Haberman R, Axelrad J, Chen A, et al. COVID-19 in immune-mediated inflammatory diseases: case series from New York. N Engl J Med 2020;383:85-88.
20. Gartshutein Y, Askasen AD, Schmidt NM, et al. COVID-19 and systemic lupus erythematosus: a case series. Lancet Rheumatol 2020;2:e452-e454.
21. Nuno L, Novella Navarro M, Bonilla G, et al. Clinical course, severity and mortality in a cohort of patients with COVID-19 with rheumatic diseases. Ann Rheum Dis 2020;79:1659-1661.
22. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
23. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-1062.
24. Favalli EG, Monti S, Ingegnoli F, Balduzzi S, Caporali R, Montecucco C. 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.
25. Quartuccio L, Valent F, Pasut E, Tascini C, De Vita S. Prevalence of COVID-19 among patients with chronic inflammatory rheumatic diseases treated with biologic agents or small molecules: a population-based study in the first two months of COVID-19 outbreak in Italy. Joint Bone Spine 2020;87:439-443.
26. Cummings MJ, Baldwin MR, Abrams, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020;395:1763-1770.
27. Petrielli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966.
28. Docherty AB, Harrison EM, Green CA, et al. Features of 2013 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. BMJ 2020;369:m1985.
29. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180:934-943.
30. Wang D, Zhang J, Lau J, et al. Mechanisms of lung disease development in rheumatoid arthritis. Nat Rev Rheumatol 2019;15:581-596.
31. Munster T, Gibbs JP, Shen D, et al. Hydroxychloroquine concentration-response relationships in patients with rheumatoid arthritis. Arthritis Rheum 2002;46:1460-1469.
32. Costedoat-Chalumeau N, Amoura Z, Hulot JS, et al. Low blood concentration of hydroxychloroquine is a marker for and predictor of disease exacerbations in patients with systemic lupus erythematosus. Arthritis Rheum 2006;54:3284-3290.
33. Memoli MJ, Czajkowski L, Reed S, et al. Validation of the wild-type influenza A human challenge model H1N1pdmMIST: an A(H1N1)pdm09 dose-finding investigational new drug study. Clin Infect Dis 2015;60:693-702.
34. Liu Y, Yan LM, Wan L, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis 2020;20:656-657.
35. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med 2020;26:672-675.
### Supplementary Table 1. Comparison between RA patients with and without COVID-19 (SARS-CoV-2 positive)

| Variable                             | Patients with COVID-19 (n = 33) | Negative controls (n = 478) | p value |
|--------------------------------------|----------------------------------|-----------------------------|---------|
| Age ≥ 60 years<sup>a</sup>           | 18 (54.6)                        | 262 (54.8)                  | 0.976   |
| Female sex<sup>a</sup>               | 26 (78.8)                        | 400 (83.7)                  | 0.465   |
| Comorbidities<sup>b</sup>            |                                  |                             |         |
| Diabetes mellitus                    | 0                                | 25 (5.2)                    | 0.178   |
| Hypertension                         | 2 (6.1)                          | 16 (3.4)                    | 0.414   |
| Cardiovascular disease               | 1 (3)                            | 20 (4.2)                    | 0.747   |
| Chronic lung disease                 | 2 (6.1)                          | 6 (1.3)                     | 0.032   |
| Chronic kidney disease               | 0                                | 3 (0.6)                     | 0.648   |
| Current medications<sup>c</sup>      |                                  |                             |         |
| Glucocorticoid                       | 22 (66.7)                        | 337 (70.5)                  | 0.641   |
| Glucocorticoid dose ≥ 10 mg/day      | 11 (33.3)                        | 161 (33.7)                  | 0.967   |
| Hydroxychloroquine                   | 20 (60.6)                        | 230 (48.1)                  | 0.165   |
| Methotrexate                         | 23 (69.7)                        | 298 (62.3)                  | 0.398   |
| Sulfasalazine                        | 14 (42.4)                        | 135 (28.2)                  | 0.083   |
| Leflunomide                          | 9 (27.3)                         | 119 (24.9)                  | 0.761   |
| Tacrolimus                           | 2 (6.1)                          | 51 (10.7)                   | 0.401   |
| TNF-α inhibitors                     | 0                                | 18 (3.8)                    | 0.256   |
| Tocilizumab                          | 0                                | 11 (2.3)                    | 0.378   |
| Abatacept                            | 2 (6.1)                          | 6 (1.3)                     | 0.032   |
| Rituximab                            | 0                                | 2 (0.4)                     | 0.710   |
| Tofactinib                           | 0                                | 2 (0.4)                     | 0.710   |

Values are presented as number (%).

RA, rheumatoid arthritis; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor.

<sup>a</sup>As recorded on the date of COVID-19 testing.

<sup>b</sup>Information on comorbidities is based on diagnostic codes (International Classification of Diseases, 10th edition [ICD-10]) in the claims data from January 1, 2015, to the test date.

<sup>c</sup>Use of medications within 3 months of the examination date was obtained from the database.
| Variable                        | Unadjusted OR (95% CI) | p value | Adjusted OR (95% CI) | p value |
|--------------------------------|------------------------|---------|----------------------|---------|
| Age ≥ 60 years                 | 0.99 (0.49–2.01)       | 0.976   | 0.90 (0.43–1.89)     | 0.771   |
| Female sex                     | 0.72 (0.30–1.73)       | 0.466   | 0.75 (0.30–1.88)     | 0.537   |
| Comorbidities                  |                        |         |                      |         |
| Hypertension                   | 1.86 (0.41–8.47)       | 0.421   |                      |         |
| Cardiovascular disease         | 0.72 (0.09–5.51)       | 0.748   |                      |         |
| Chronic lung disease           | 5.08 (0.98–26.19)      | 0.052   | 6.07 (1.10–33.59)    | 0.039   |
| Current medications            |                        |         |                      |         |
| Glucocorticoid                 | 0.84 (0.40–1.77)       | 0.641   |                      |         |
| Glucocorticoid dose ≥ 10 mg/day| 0.99 (0.47–2.08)       | 0.967   |                      |         |
| Hydroxychloroquine             | 1.66 (0.81–3.41)       | 0.169   | 1.51 (0.69–3.32)     | 0.304   |
| Methotrexate                   | 1.39 (0.65–2.99)       | 0.400   |                      |         |
| Sulfasalazine                  | 1.87 (0.91–3.84)       | 0.087   | 1.59 (0.72–3.50)     | 0.252   |
| Leflunomide                    | 1.13 (0.51–2.50)       | 0.761   |                      |         |
| Tacrolimus                     | 0.54 (0.13–2.32)       | 0.408   |                      |         |
| Abatacept                      | 5.08 (0.98–26.19)      | 0.052   | 5.49 (1.02–29.66)    | 0.048   |

COVID-19, coronavirus disease 2019; RA, rheumatoid arthritis; OR, odds ratio; CI, confidence interval.
### Supplementary Table 3. Comparison between SLE patients with and without COVID-19 (SARS-CoV-2 positive)

| Variable                        | Patients with COVID-19 (n = 20) | Negative controls (n = 263) | p value |
|---------------------------------|---------------------------------|-----------------------------|---------|
| Age ≥ 50 years<sup>a</sup>      | 15 (75.0)                       | 180 (68.4)                  | 0.541   |
| Female sex<sup>a</sup>          | 16 (80.0)                       | 219 (83.3)                  | 0.707   |
| Comorbidities<sup>b</sup>       |                                 |                             |         |
| Diabetes mellitus               | 0                               | 3 (1.1)                     | 0.631   |
| Hypertension                    | 0                               | 5 (1.9)                     | 0.534   |
| Cardiovascular disease          | 0                               | 6 (2.3)                     | 0.495   |
| Chronic lung disease            | 1 (5.0)                         | 2 (0.8)                     | 0.074   |
| Chronic kidney disease          | 0                               | 2 (0.8)                     | 0.696   |
| Current medications<sup>c</sup>|                                 |                             |         |
| Glucocorticoid                  | 13 (65.0)                       | 156 (59.3)                  | 0.617   |
| Glucocorticoid dose ≥ 10 mg/day | 13 (65.0)                       | 144 (54.8)                  | 0.374   |
| Hydroxychloroquine              | 3 (15.0)                        | 65 (24.7)                   | 0.327   |
| Methotrexate                    | 1 (5.0)                         | 10 (3.8)                    | 0.789   |
| Tacrolimus                      | 0                               | 6 (2.3)                     | 0.495   |

Values are presented as number (%).

SLE, systemic lupus erythematosus; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

<sup>a</sup>As recorded on the date of COVID-19 testing.

<sup>b</sup>Information on comorbidities is based on diagnostic codes (International Classification of Diseases, 10th edition [ICD-10]) in the claims data from January 1, 2015, to the test date.

<sup>c</sup>Use of medications within 3 months of the examination date was obtained from the database.
### Supplementary Table 4. Factors associated with COVID-19 in patients with SLE

| Variable                  | Unadjusted OR (95% CI) | \( p \) value | Adjusted OR (95% CI) | \( p \) value |
|---------------------------|------------------------|---------------|----------------------|---------------|
| Age ≥ 50 years            | 1.38 (0.49–3.93)       | 0.543         | 1.69 (0.54–5.26)     | 0.364         |
| Female sex                | 0.80 (0.26–2.52)       | 0.708         | 0.76 (0.24–2.39)     | 0.634         |
| **Comorbidities**         |                        |               |                      |               |
| Chronic lung disease      | 6.87 (0.60–79.22)      | 0.123         | 10.70 (0.78–146.03)  | 0.076         |
| **Current medications**   |                        |               |                      |               |
| Glucocorticoid            | 1.27 (0.49–3.30)       | 0.618         |                      |               |
| Glucocorticoid dose ≥ 10 mg/day | 1.53 (0.59–3.97) | 0.377         |                      |               |
| Hydroxychloroquine        | 0.54 (0.15–1.89)       | 0.334         |                      |               |
| Methotrexate              | 1.33 (0.16–10.96)      | 0.790         |                      |               |

COVID-19, coronavirus disease 2019; SLE, systemic lupus erythematosus; OR, odds ratio; CI, confidence interval.