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

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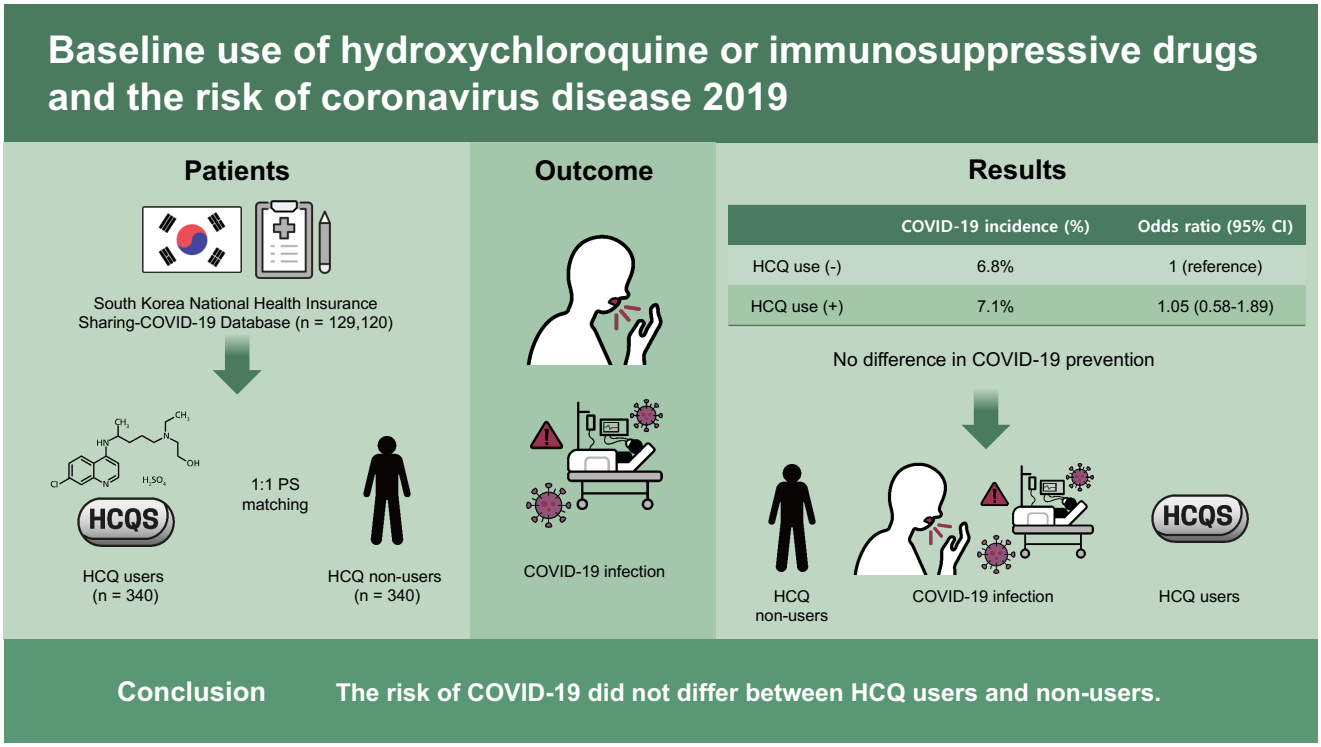

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Background/Aims: The preventive role of hydroxychloroquine (HCQ) on coronavirus disease 2019 (COVID-19) remains unclear. The aim of this study was to examine the effects of HCQ and other immunosuppressive drugs on the incidence of COVID-19.

Methods: The data were collected from the South Korea National Health Insurance Sharing-COVID-19 database. All individuals who underwent nasopharyngeal and oropharyngeal swab tests for COVID-19 from January 2020 to May 2020 are included. The association between COVID-19 risk and HCQ use was examined in a propensity score-matched population. Factors associated with COVID-19 were identified using multiple logistic regression analysis.

Results: Total 8,070 patients with COVID-19 and 121,050 negative controls were included from the database. Among all participants, 381 were HCQ users. In a propensity score-matched population, the incidence of COVID-19 was 7.1% in HCQ users and 6.8% in non-users. The odds ratio (OR) for HCQ use was 1.05 with a 95% confidence interval (CI) of 0.58 to 1.89. Among the subpopulation of patients with rheumatoid arthritis (RA), 33 were diagnosed with COVID-19 and 478 were not. Use of HCQ, glucocorticoids, or other immunosuppressive drugs was not associated with COVID-19 risk, whereas abatacept use was. Chronic lung disease was an independent risk factor for COVID-19 diagnosis in patients with RA (adjusted OR, 6.07; 95% CI, 1.10 to 33.59).

Conclusions: The risk of COVID-19 did not differ between HCQ users and non-users. Glucocorticoids, conventional disease-modifying antirheumatic drugs (DMARDs), and biological DMARDs other than abatacept did not increase the risk of COVID-19.

Keywords: COVID-19; SARS-CoV-2; Hydroxychloroquine; Immunosuppressive agents; Antirheumatic agents

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 immunosuppressive drugs on the incidence 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

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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-

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 (0.01)	< 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 (0.02)	< 0.001	31 (9.1)	24 (7.1)	0.325
TNF-α inhibitors	12 (3.2)	29 (0.02)	< 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.

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).

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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.

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-

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, medial chart review was not possible, and other factors,

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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.

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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[a]	18 (54.6)	262 (54.8)	0.976
Female sex[a]	26 (78.8)	400 (83.7)	0.465
Comorbidities[b]			
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[c]			
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
Tofacitinib	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.

[a]As recorded on the date of COVID-19 testing.

[b]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.

[c]Use of medications within 3 months of the examination date was obtained from the database.

Supplementary Table 2. Factors associated with COVID-19 in patients with RA

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.

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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[a]	15 (75.0)	180 (68.4)	0.541
Female sex[a]	16 (80.0)	219 (83.3)	0.707
Comorbidities[b]			
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[c]			
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.

[a]As recorded on the date of COVID-19 testing.

[b]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.

[c]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.

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