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The Efficacy of Long-Term Hydroxychloroquine Use in the Prevention of COVID-19: A Retrospective Cohort Study

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Abstract. The use of hydroxychloroquine (HCQ) in the prevention or treatment of COVID-19 remains controversial due to the insufficient supporting evidence and clinical studies indicating that it does not reduce COVID-19 mortality. Its potential protective effects against SARS-CoV-2 are still unclear. Big data resources, such as MarketScan database containing over 30 million insured participants annually, have not been used systematically to assess the association between long-term HCQ use and the risk of COVID-19. This retrospective study aimed to determine the protective effect of HCQ using the MarketScan database. We examined COVID-19 incidence from January to September 2020 among adult patients with systemic lupus erythematosus or rheumatoid arthritis who had received HCQ for at least 10 months in 2019 compared to those who did not. Propensity score matching was used to control for confounding variables and make the HCQ and non-HCQ groups comparable in this study. After matching at the ratio of 1:2, the analytical dataset comprised 13,932 patients who received HCQ for over 10 months and 27,754 HCQ-naïve patients. Multivariate logistic regression showed that long-term HCQ use was associated with a lower likelihood of COVID-19 in patients who had been receiving HCQ for over 10 months (OR=0.78, 95% CI: 0.69-0.88). These findings suggest that long-term HCQ use may provide protection against COVID-19.

Keywords. Hydroxychloroquine, COVID-19, big data

1. Introduction

The emergence of COVID-19 in early 2020 led to a global effort to identify potential treatments for the disease. Among these, hydroxychloroquine (HCQ) was approved for Emergency Use Authorization (EUA) to treat hospitalized COVID-19 patients based on initial in vitro studies suggesting its efficacy in inhibiting SARS-CoV-2 infection [1]. However, subsequent observational studies [2] and randomized clinical trials [3] showed that HCQ did not reduce mortality or symptom severity in COVID-19 patients nor prevent COVID-19 infection following exposure. Meanwhile, randomized trials have also shown that HCQ did not reduce symptom severity in non-hospitalized patients with early, mild COVID-19 [4]. In addition, trials indicated that HCQ did not prevent COVID-19 infection within a few days after high-risk or moderate-risk exposure to COVID-19 [5].

Despite this, some studies have suggested that countries with high rates of malaria, and hence high rates of HCQ use, had lower COVID-19 infection prevalence [6,7], bringing up the question of whether long-term HCQ use could have a preventive effect against COVID-19. To address this question, we examined the association between long-term HCQ use and COVID-19 using the IBM® MarketScan® Research Databases.

2. Method

2.1. Study setting and population.

The study aimed to investigate whether long-term use of HCQ could prevent SARS-CoV-2 infection. To achieve this, we conducted a retrospective cohort study using the 2019-2020 IBM® MarketScan® Research Database containing de-identified commercial claims (inpatient, outpatient, emergency and outpatient pharmacy) covering more than 30 million covered lives across the US.

Because HCQ is a long-term treatment in systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) recommended by the current guidelines [8], the study only included adult patients with SLE or RA. The exposure of interest was the long-term use of HCQ, defined as HCQ's total supply for more than 10 months in 2019. Thus 22,989 patients who had received HCQ's total supply for less than 10 months in 2019 were excluded. The outcome was the occurrence of COVID-19 diagnoses in outpatient or hospital settings between January 2020 and September 2020.

For each patient, we collected relevant variables, including patients' age, sex, outpatient and hospital diagnoses, outpatient drug prescriptions (including drug name and supply days), as well as Charlson Comorbidity Index (CCI) [9], which was calculated based on the patients' historical diagnoses.

2.2. Statistical analysis

To examine the relationship between long-term HCQ use and COVID-19 diagnosis, we assessed the associations between HCQ exposure and collected patient characteristics using chi-square tests for categorical variables. Then the multivariate logistic regression model was used to explore the association between COVID-19 diagnosis and long-term HCQ use, adjusting for covariates, including age, sex, and CCI. To further minimize the impact of selection bias and confounding effects, we repeated a secondary analysis using the propensity-score matched population. Specifically, the nearest-neighbor method was used to generate the 1:2 propensity-score matched samples.

All analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC). A two-sided p-value of < 0.05 was considered as statistically significant.

3. Results

A total of 96,106 SLE or RA patients who did not receive HCQ and 13,932 patients who received long-term HCQ were included in our analysis based on the selection criteria. The distribution of patients' characteristics is presented in Table 1 for both the unmatched and 1:2 propensity-score matched population. The logistic regression models, adjusting

for age, sex, and CCI, showed a significant difference in SARS-CoV-2 infection rates between long-term HCQ users and non-users with an odds ratio of 0.79 (95% CI: 0.69-0.91). In the matched study population, a similar significant difference in COVID-19 diagnosis was found with an odds ratio of 0.78 (95% CI: 0.69-0.88). These results suggested that long-term HCQ use may be associated with a reduced incidence of COVID-19 among SLE or RA patients.

4. Discussion

Despite the promising results, it is important to acknowledge the limitations of our retrospective cohort study. First, this analysis did not consider racial groups due to the lack of race/ethnicity information in the IBM® MarketScan® Databases. Second, the potential risks of side effects or adverse effects from long-term HCQ use as a prophylaxis for SARS-CoV-2 in individuals without autoimmune diseases are currently unknown. Finally, individuals with autoimmune diseases have weakened immune systems, and medications used to treat these conditions may further suppress their immune response, potentially increasing their risk of untoward consequences.

5. Conclusions

Our analysis of SLE or RA patients who had received long-term HCQ use revealed a significant reduction in the incidence of COVID-19 compared to those who did not receive HCQ (OR=0.79, 95% CI: 0.69-0.91). These findings are consistent with previous studies that have suggested that HCQ may be associated with a reduction in COVID-19 mortality and viral load in patients with the disease [10, 11].

Future research should investigate the potential risks and benefits of HCQ prophylaxis in individuals without autoimmune diseases. These findings may help guide clinical decision-making and improve patient outcomes.

Table 1. Characteristics of Patients Receiving or Not Receiving Hydroxychloroquine, before and after Propensity-Score Matching.

	Unmatched Population			1:2 Propensity Score matched Population		
Variables	**Non-HCQ** N=96,106 (87.3%)	**HCQ >=10 months** N=13,932 (12.7%)	**P-value**	**Non-HCQ** N=27,864 (66.7%)	**HCQ >=10 months** N=13,932 (33.3%)	**P-value**
Age Group			<.0001			0.88
18-40	14241(14.8%)	1974(14.2%)		3871(13.9%)	1974(14.2%)	
41-54	31416(32.7%)	4691(33.7%)		9381(33.7%)	4691(33.7%)	
55-64	36562(38.0%)	5695(40.9%)		11468(41.2%)	5695(40.9%)	
65 +	13887(14.5%)	1572(11.2%)		3144(11.2%)	1572(11.2%)	
Sex			<.0001			0.99
Male	23505(24.6%)	1999(14.4%)		3997(14.3%)	1999(14.6%)	
Female	72601(75.4%)	11933(85.6%)		23867(85.7%)	11933(85.6%)	
CCI			<.0001			1.00
0	27211(28.3%)	2022(14.5%)		4044(14.5%)	2022(14.5%)	
1	43896(45.7%)	5729(41.1%)		11458(41.1%)	5729(41.1%)	

>=2	24999(26.0%)	6181(44.4%)	12362(44.4%)	6181(44.4%)

Table 2. Associations between HCQ Use and COVID-19 diagnosis, adjusting for age, sex, and CCI.

	Effect	OR	95% CI		P-value
Unmatched Population (Adjusting for Age, CCI)					
HCQ Use	HCQ (vs. Non-HCQ)	**0.78**	0.69	0.88	**<.0001**
Age	41-54 (vs. 18-40)	0.98	0.88	1.09	0.70
	55-64 (vs. 18-40)	0.83	0.74	0.92	0.001
	65 and older (vs. 18-40)	0.51	0.44	0.59	<.0001
CCI	1 (vs. 0)	1.03	0.94	1.13	0.49
	>=2 (vs. 0)	1.16	1.05	1.29	0.004
Propensity-Score Matched Population (Adjusting for Age, Sex, CCI)					
HCQ Use	HCQ (vs. Non-HCQ)	**0.79**	0.69	0.91	**0.0007**
Age	41-54 (vs. 18-40)	1.02	0.84	1.23	0.86
	55-64 (vs. 18-40)	0.88	0.73	1.05	0.16
	65 and older (vs. 18-40)	0.48	0.37	0.64	<.0001
Sex	Male (vs. Female)	1.15	0.97	1.37	0.12
CCI	1 (vs. 0)	1.22	0.99	1.50	0.06
	>=2 (vs. 0)	1.42	1.16	1.74	0.0007

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