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Antimalarials Are Not Effective as Pre-Exposure Prophylaxis for COVID-19: A Retrospective Matched Control Study

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ABSTRACT

The early phase of the COVID-19 pandemic prompted a repurposing of antiviral and immunomodulatory drugs as investigational therapeutics, including hydroxychloroquine and chloroquine. While antimalarials have been well-refuted as a treatment for COVID-19, data on these drugs' role in preventing SARS-CoV-2 infection as pre-exposure prophylaxis is more limited. We investigated the efficacy of antimalarial drugs as pre-exposure SARS-CoV-2 prophylaxis in a US tertiary-care center. We identified all adult patients exposed to antimalarials with active prescriptions from July 1, 2019 to February 29, 2020 and exact-matched antimalarial-treated study patients with controls on age, sex, race, and Charleston Comorbidity Index. We used multivariable logistic regression to calculate the odds ratio (OR) of COVID-19 diagnosis by antimalarial exposure, adjusting for demographics, comorbidities, local infection rates, and specific conditions identified in early studies as risk factors for COVID-19. There were 3,074 patients with antimalarial prescriptions and 58,955 matched controls. Hydroxychloroquine represented 98.8% of antimalarial prescriptions. There were 51 (1.7%) infections among antimalarial-exposed and 973 (1.6%) among controls. No protective effect for SARS-CoV-2 infection was demonstrated among antimalarial-exposed patients in the multivariate model (OR=1.06, 95% CI 0.80-1.40, *P*=0.70). These findings corroborate prior work demonstrating that hydroxychloroquine and related antimalarials do not have a role in protection against SARS-CoV-2.

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To the Editor:

The early phase of the COVID-19 pandemic prompted a repurposing of antiviral and immunomodulatory drugs as investigational therapeutics, including hydroxychloroquine and chloroquine.[1] Despite an early interest in these potentially preventative medications given positive in vitro findings,[2] randomized control trials of hydroxychloroquine as post-exposure prophylaxis did not reveal differences in infection susceptibility; appropriately, antimalarials are not recommended for treatment of COVID-19.[3]

While antimalarials have been well-refuted as a treatment for COVID-19, data on these drugs' role in preventing SARS-CoV-2 infection as pre-exposure prophylaxis is more limited. Hydroxychloroquine is frequently prescribed for dermatologic and rheumatologic diseases, and thus data on this drug's pre-exposure impact on SARS-CoV-2 risk is of great importance to the practicing dermatologist. We investigated the efficacy of antimalarial drugs as pre-exposure SARS-CoV-2 prophylaxis in a US tertiary-care center.

MATERIALS AND METHODS

We included all adult patients with at least one prescription for chloroquine, hydroxychloroquine, or quinacrine from July 1, 2019 to February 29, 2020 (limiting prescriptions to those started before the pandemic onset) in the MassGeneral Brigham Enterprise Data Warehouse and Research Patient Data Registry. We exact-matched antimalarial-treated study patients with controls on age, sex, race, and Charleston Comorbidity Index. Additional collected variables included zip codes (used to estimate income using 2010 US Census), and medical history using ICD-9/ICD-10

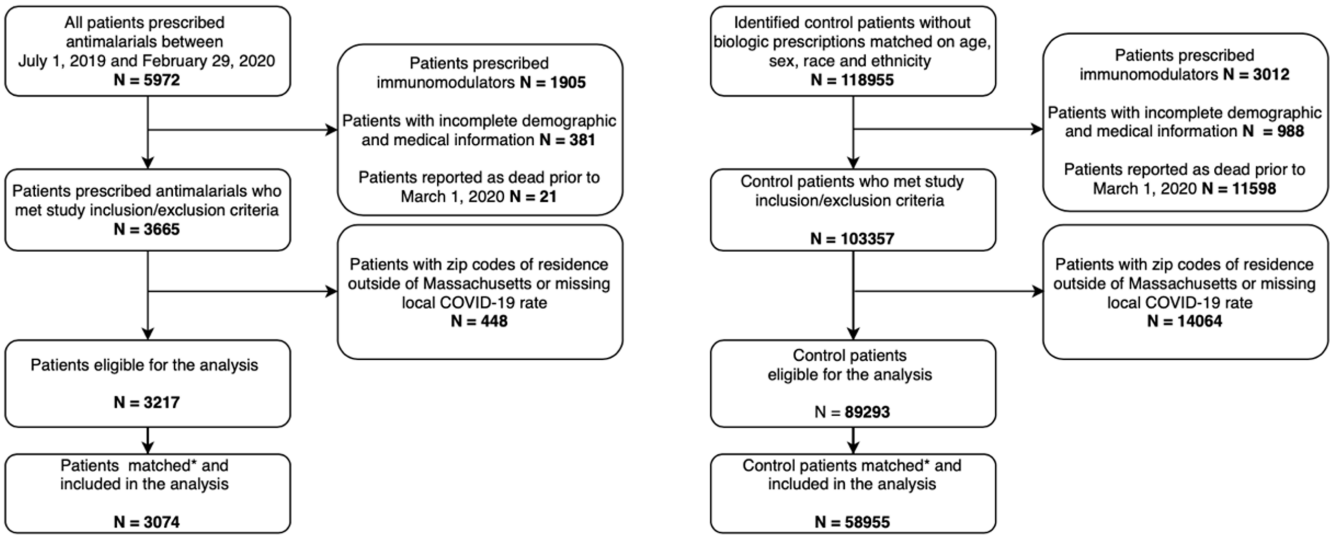
TABLE 1.

Multivariable Logistic Regression of the Risk of SARS-CoV-2 (COVID-19) PCR Test Positivity

	Antimalarials Group N = 3074	Matched Control Group N = 58955	*P*-value	OR	95% CI	*P*-value
Age group N (%)	--	--	1.00	--	--	--
18-44	718 (23.4%)	13770 (23.4%)	--	ref*	ref*	ref*
45-64	1272 (41.4%)	24395 (41.4%)	--	0.92	0.76 – 1.11	0.38
65-74	637 (20.7%)	12217 (20.7%)	--	0.54	0.42 – 0.70	< 0.001
≥75	447 (14.5%)	8573 (14.5%)	--	0.90	0.69 – 1.16	0.42
Female sex N (%)	2611 (84.9%)	50075 (84.9%)	1.00	1.20	1.01 – 1.43	0.04
Race and ethnicity N (%)	--	--	1.00	--	--	--
White Non-Hispanic	47678 (80.9%)	2486 (80.9%)	--	ref*	ref*	ref*
Asian/PI Non-Hispanic	2033 (3.4%)	106 (3.4%)	--	0.69	0.45 – 1.07	0.10
Black Non-Hispanic	4296 (7.3%)	224 (7.3%)	--	1.52	1.25 – 1.84	< 0.001
Other Non-Hispanic	2033 (3.4%)	106 (3.4%)	--	1.27	0.96 – 1.68	0.10
Hispanic	1285 (2.2%)	67 (2.2%)	--	0.78	0.50 – 1.22	0.27
Unknown	1630 (2.8%)	85 (2.8%)	--	0.65	0.38 – 1.12	0.12
CCI grade N (%)	--	--	1.00	--	--	--
Mild (1-2)	1275 (41.5%)	24453 (41.5%)	--	ref*	ref*	ref*
Moderate (3-4)	799 (26.0%)	15324 (26.0%)	--	1.12	0.92 – 1.38	0.26
Severe (≥5)	1000 (32.5%)	19179 (32.5%)	--	1.90	1.48 – 2.45	< 0.001
Comorbidity N (%)						
Hypertension	1130 (36.8%)	20308 (34.4%)	< 0.01	1.41	1.21 – 1.63	< 0.001
Congestive heart failure	231 (7.5%)	4771 (8.1%)	0.25	1.75	1.47 – 2.09	< 0.001
Diabetes mellitus	382 (12.4%)	11376 (19.3%)	< 0.001	1.15	0.99 – 1.34	0.07
COPD	499 (16.2%)	11622 (19.7%)	< 0.001	1.23	1.06 – 1.42	0.01
Other chronic pulmonary disease	729 (23.7%)	18089 (30.7%)	< 0.001	0.94	0.82 – 1.07	0.34
Renal disease	310 (10.1%)	6069 (10.3%)	0.71	1.23	1.03 – 1.47	0.02
Liver disease	416 (13.5%)	11344 (19.2%)	< 0.001	0.93	0.80 – 1.09	0.38
Hematologic cancer	122 (4.0%)	2601 (4.4%)	0.24	0.62	0.44 – 0.87	0.01
Solid organ cancer	499 (16.2%)	15953 (27.1%)	< 0.001	0.87	0.74 – 1.02	0.10
Metastatic cancer	81 (2.6%)	3643 (6.2%)	< 0.001	0.59	0.43 – 0.83	< 0.01
Inflammatory bowel disease	76 (2.5%)	1617 (2.7%)	0.37	0.70	0.46 – 1.06	0.09
Rheumatic disease	1939 (63.1%)	3768 (6.4%)	< 0.001	0.79	0.62 – 0.99	0.05
Socio-geographic factors	3 (5.8%)	83 (8.5%)	0.53	--	-	--
County SARS-CoV-2 PCR test positivity rate per 100 Mean (SD)	1.46 (0.91)	1.59 (1.11)	< 0.001	1.24	1.19 – 1.30	< 0.001
Median income ($1,000x) Mean (SD)	81.7 (2.9)	79.3 (2.9)	< 0.001	0.99	0.96 – 1.01	0.38
COVID-19 positive N (%)	51 (1.7%)	973 (1.6%)	0.97	N/A	-	--
Died N (% of PCR-positive patients)	3 (5.8%)	83 (8.5%)	0.53	N/A	--	--

Abbreviations: CCI = Charlson Comorbidity Index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; OR = odds ratio; PCR = polymerase chain reaction; PI = Pacific Islander; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; and SD = standard deviation.

FIGURE 1. Study flow diagram for selection of antimalarials-exposed cases and matched controls.



*Patients treated with antimalarials were matched with controls using exact matching on age, gender, race, and age adjusted numerical Charleston Comorbidity Index (CCI) score.

Abbreviations: COVID-19 = coronavirus disease 2019

codes. Massachusetts Department of Public Health and COVID-19 Dashboard provided data on COVID-19 diagnosis status, and baseline county rates, respectively. Patients with incomplete data, non-Massachusetts zip codes, and prescriptions for other immunomodulator drugs were excluded (see Supplemental Table at https://data.mendeley.com/datasets/5z2vdhzbs4/1). We used multivariable logistic regression to calculate the odds ratio (OR) of COVID-19 diagnosis by antimalarial exposure, adjusting for demographics, comorbidities, local infection rates, and specific conditions identified in early studies as risk factors for COVID-19.[4,5] Pearson's chi-square and two-tailed t-tests were used for pairwise comparisons of categorical and continuous variables, respectively.

RESULTS

There were 3,074 patients with antimalarial prescriptions and 58,955 matched controls (Figure 1). Hydroxychloroquine represented 98.8% of antimalarial prescriptions (Table 1). There were 51 (1.7%) infections among antimalarial-exposed and 973 (1.6%) among controls. No protective effect for SARS-CoV-2 infection was demonstrated among antimalarial-exposed patients in the multivariate model (OR=1.06, 95% CI 0.80-1.40, *P*=0.70).

Ages 65-74 were less likely to have confirmed COVID-19 diagnosis than patients aged 18-44 years (OR=0.61 [0.48-0.79], *P*<0.001). Sex did not affect susceptibility (OR=1.05 [0.88-1.24], *P*=0.61). Black patients had a higher infection risk than white patients (OR=1.64 [1.35-1.98], *P*<0.001). Severe comorbidity burden also increased SARS-CoV-2 infection risk (OR=2.32 [1.92-2.81], *P*<0.001). Local infection rates predicted SARS-CoV-2 infection (OR=1.26 [1.21-1.32], *P*<0.001), while median income by zip code did not (OR=0.98 [0.96-1.01], *P*=0.18).

Among the comorbidities analyzed, hypertension (OR=1.41 [1.21-1.63], *P*<0.001), congestive heart failure (OR 1.75 [1.47-2.09], *P*<0.001), COPD (OR=1.23 [1.06-1.42], *P*=0.01), and renal disease (OR=1.23 [1.03-1.47], *P*=0.02) were identified as independent risk factors for COVID-19. Hematologic cancer (OR=0.62 [0.44-0.87], *P*=0.01), metastatic cancer (OR=0.59 [0.43-0.83], *P*<0.01), and rheumatic disease (OR=0.79 [0.62-0.99], *P*=0.05) were found to have a protective effect.

DISCUSSION

We found that pre-pandemic antimalarial prescriptions were not protective of COVID-19 diagnosis among queried individuals, consistent with past evidence demonstrating these agents' lack of efficacy as post-exposure prophylaxis.[3]

Antimalarials are frequently used to manage chronic cutaneous and systemic autoimmune diseases such as rheumatoid arthritis, lupus erythematosus, and juvenile idiopathic arthritis.[6] Interestingly, we identified that a history of rheumatic disease – as well as hematologic cancer or metastatic cancer – was

independently significantly associated with a lower risk for SARS-CoV-2 infection. Given that the treatment of rheumatic disease and hematologic/metastatic malignancy – with systemic immunosuppression and chemotherapy, respectively – can plausibly reduce the immune response to SARS-CoV-2, patients with a history of these diseases may engage in protective behaviors to limit their potential exposure to infection, as has been reported amongst patients with rheumatic diseases.[7,8]

Limitations include Massachusetts-restricted data and a single-center perspective. Study patients who were prescribed antimalarials were more likely to live in zip codes with lower COVID-19 incidence rates and higher average incomes, which may be confounded by differential access to care.

Antimalarial agents – particularly hydroxychloroquine – received significant consideration as a potential treatment for or prophylactic drug against COVID-19.[2] We demonstrate that, amongst patients with antimalarial prescriptions predating the COVID-19 pandemic in Massachusetts, antimalarials did not significantly prevent SARS-CoV-2 infection. These findings corroborate that hydroxychloroquine and related antimalarials do not have a role in protection against SARS-CoV-2.

DISCLOSURES

The authors above have no conflicts of interest to disclose for the following work.

IRB approval status: This study was approved by the Institutional Review Boards at Mass General Brigham (Protocol 2020P001191) and Massachusetts Department of Public Health (Protocol 1606024-2).

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