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No clinical benefit in mortality associated with hydroxychloroquine treatment in patients with COVID-19



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ABSTRACT

Background: The use of hydroxychloroquine (HCQ), with or without concurrent administration of azithromycin (AZM), for treatment of COVID-19 has received considerable attention. The purpose of this study was to determine whether HCQ administration is associated with improved mortality in COVID-19 patients.

Methods: We conducted a retrospective analysis of data collected during the care process for COVID-19 positive patients discharged from facilities affiliated with a large healthcare system in the United States as of April 27, 2020. Patients were categorized by treatment with HCQ (in addition to standard supportive therapy) or receipt of supportive therapy with no HCQ. Patient outcomes were evaluated for in-hospital mortality. Patient demographics and clinical characteristics were accounted for through a multivariable regression analysis.

Results: A total of 1669 patients were evaluated (no HCQ, n = 696; HCQ, n = 973). When adjusting for patient characteristics, receipt of AZM, and severity of disease at admission, there was no beneficial effect of receipt of HCQ on the risk of death. In this population, there was an 81% increase in the risk of mortality among patients who received HCQ at any time during their hospital stay versus no HCQ exposure (OR: 1.81, 95% CI: 1.20–2.77, p = 0.01).

Conclusions: In this retrospective analysis, we found that there was no benefit of administration of HCQ on mortality in COVID-19 patients. These results support recent changes to clinical trials that discourage the use of HCQ in COVID-19 patients.

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Introduction

The outbreak of coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization on March 11, 2020. As of June 22, 2020, a total of 2,275,645 COVID-19 cases and 119,923 related deaths had been reported in the United States ([Centers for Disease Control and Prevention, 2020](#)). Reports from around the world indicate that this disease will continue to spread with the potential to cause severe illness in 10%–20% of those infected and to lead to hospitalization, ICU admission, ventilator support, and death.

Treatment for COVID-19 disease is primarily limited to supportive care and management of symptoms. Numerous treatments that attempt to reduce viral load and change the duration or trajectory of the disease are under investigation and recommendations are based on limited evidence or extrapolated from the treatment of other coronaviruses. As part of this, considerable attention has been paid, both in the press and in the scientific community, to the use of chloroquine and hydroxychloroquine (HCQ), with or without concomitant administration of azithromycin (AZM), due to its ability to inhibit other coronaviruses.

Chloroquine has been associated with improved patient outcomes and shortened hospital stay for patients with COVID-19 ([Keyaerts et al., 2009](#); [Vincent et al., 2005](#)). HCQ has a similar proposed mechanism of action as chloroquine ([Yao et al., 2020](#)) and clinical trials are underway to investigate the use as a treatment option for COVID-19 ([Massachusetts General Hospital & National Heart, 2020](#); [National Institute of Allergy and Infectious](#)

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Diseases (NIAID), 2020; Shanghai Public Health Clinical Center, 2020). Preliminary results have suggested that HCQ in combination with AZM can reduce viral load in patients with confirmed COVID-19 disease (Gautret et al., 2020a). Further confirmation is needed regarding the effect of HCQ on outcomes for COVID-19 patients (Gautret et al., 2020b; Molina et al., 2020; Perinel et al., 2020) as recent reports have emphasized the potential harm of this treatment and the risk for severe QT prolongation and mortality (Borba et al., 2020; Hernandez et al., 2020). Several large scale clinical trials have been initiated, and some paused due to developing evidence. This uncertainty and high-profile retractions has contributed to recent guidelines and recommendations related to the use of HCQ outside of controlled clinical trials (Bhimraj et al.,

2020; Food and Drug Administration, 2020b; National Institutes of Health, 2020).

Here we provide a retrospective analysis of the use of HCQ in COVID-19 patients within a system of community hospitals in the United States. We performed an initial assessment of outcomes among those patients given HCQ, and created a multivariable model describing risk factors of severe outcomes in patients who received treatment in comparison with those that received supportive therapy without HCQ. These results can indicate whether use of this treatment outside of clinical trials is warranted, as well as help with the targeting of HCQ treatment to maximize benefit while reducing the risk of adverse events.

Table 1
Demographic characteristics of COVID-19 patients by HCQ status.

	No HCQ (control) (N = 696)	Received HCQ ^a (treated) (N = 973)	p value
Age At Admission			0.17
Mean (SD)	61.3 (17.8)	60.2 (16.6)	
Median [Min, Max]	63.0 [18.0, 100]	60.0 [19.0, 103]	
Race			0.58
white	318 (45.7%)	467 (48.0%)	
asian	31 (4.5%)	36 (3.7%)	
black	208 (29.9%)	296 (30.4%)	
other	105 (15.1%)	139 (14.3%)	
unknown	34 (4.9%)	35 (3.6%)	
Ethnicity			0.09
Not Hispanic Or Latino	518 (74.4%)	694 (71.3%)	
Hispanic Or Latino	141 (20.3%)	238 (24.5%)	
Unknown	37 (5.3%)	41 (4.2%)	
Sex			0.44
Female	346 (49.7%)	464 (47.7%)	
Male	350 (50.3%)	509 (52.3%)	
Smoking status (self-identified) ^a			0.17
never smoked	442 (63.5%)	681 (70.0%)	
former smoker	127 (18.2%)	160 (16.4%)	
smoker	33 (4.7%)	39 (4.0%)	
unknown	64 (9.2%)	73 (7.5%)	
No data available	30 (4.3%)	20 (2.1%)	
BMI			0.27
Mean (SD)	30.8 (9.27)	33.2 (65.0)	
Median [Min, Max]	29.0 [13.7, 143]	29.9 [13.8, 2050]	
Weighted Elixhauser score			0.03
Mean (SD)	6.41 (7.31)	5.62 (7.52)	
Median [Min, Max]	5.00 [-14.0, 36.0]	5.00 [-10.0, 44.0]	
First MEWS score ^a			0.68
Mean (SD)	1.56 (1.15)	1.53 (1.06)	
Median [Min, Max]	1.00 [0, 8.00]	1.00 [0, 7.00]	
Change in average MEWS 12–48 hours ^a			0.21
Mean (SD)	-0.0636 (0.901)	-0.00879 (0.876)	
Median [Min, Max]	0 [-3.00, 5.00]	0 [-3.67, 5.50]	
Length of stay (days)			< 0.01
Mean (SD)	5.13 (3.69)	7.95 (5.49)	
Median [Min, Max]	4.00 [1.00, 27.0]	7.00 [1.00, 49.0]	
Severity on admission ^a			0.73
mild	648 (93.1%)	914 (93.9%)	
moderate	42 (6.0%)	50 (5.1%)	
severe	6 (0.9%)	9 (0.9%)	
Discharge Disposition			0.42
Expired	56 (8.0%)	101 (10.4%)	
Home	543 (78.0%)	745 (76.6%)	
Hospice	29 (4.2%)	41 (4.2%)	
Transferred	68 (9.8%)	86 (8.8%)	
Seven-day readmission ^a			< 0.01
Not readmitted	660 (94.8%)	957 (98.4%)	
Readmitted	36 (5.2%)	16 (1.6%)	

^a Note: Receipt of HCQ could occur at any time during their hospital stay. Smoking status was indicated through point of contact queries; unknown status was an option for selection in this query. Change in MEWS score represents the difference in scores for a patient from the average available MEWS scores between 0–24 hours after admission (12 -h score) and the average available MEWS scores between 36–60 hours after admission (48 -h score). Severity on admission was determined by the highest level of care required within 8 h of admission (mild = no ICU or mechanical ventilation; moderate = ICU but no mechanical ventilation; severe = required mechanical ventilation). Readmission data only includes those patients who were readmitted to a facility affiliated with the healthcare system in this analysis. P values represent test of means (two-sided *t*-test for continuous variables, chi square analysis for discrete variables).

Methods

Setting

We conducted this retrospective analysis using data collected as a part of routine care within acute care facilities affiliated with HCA Healthcare. This large healthcare system consists primarily of community hospitals in the United States. Collectively, these facilities provide approximately 5% of US hospital services. Facilities are located in 21 states, with a concentration in the southern part of the country.

Data from clinical care activities in affiliated facilities are collected via the electronic health record and collated within a clinical data warehouse (CDW). Data streams are processed and made available for retrospective analysis and for real-time data products to support clinical care activities (Guy et al., 2020).

Data definitions

Data were collected from the CDW for patients with confirmed COVID-19 disease and discharge dates through April 27, 2020.

COVID-19 status was determined by the presence of at least one documented positive detection of SARS-CoV-2 by reverse transcriptase–polymerase chain reaction (RT-PCR); this included patients with positive results from outside of the affiliated system that were documented at admission or transfer.

Patient characteristics were collected from the electronic health record. Basic demographics included age, sex, race, ethnicity, body mass index (BMI), and self-reported smoking status (current smoker, former smoker, never smoker, unknown status). Van Walraven weighted Elixhauser comorbidity index was calculated to incorporate patient comorbidities. Modified Early Warning Score (MEWS) was calculated automatically within the electronic health record using vital signs as they were collected and entered. Seven-day readmission included only those patients who were readmitted to a facility affiliated with the HCA Healthcare system, as these were the only readmission data available.

Patient severity was defined as the level of care a patient received within 8 h of admission. Patients classified as “mild” disease had no documentation of care within a critical care unit within 8 h of admission. Patients classified as “moderate” disease required intensive care within a critical care unit but not

Table 2
Demographics and clinical characteristics of patients with in-hospital mortality by HCQ + AZM treatment status.

	No HCQ (control) Died (N = 56)	Received HCQ ^a (treated) Died (N = 101)	P value
Age At Admission			< 0.01
Mean (SD)	80.1 (12.2)	73.2 (14.4)	
Median [Min, Max]	83.0 [30.0, 100]	75.0 [37.0, 98.0]	
Race			0.03
White	29 (51.8%)	61 (60.4%)	
Asian	4 (7.1%)	0 (0%)	
Black	16 (28.6%)	30 (29.7%)	
Other	2 (3.6%)	7 (6.9%)	
Unknown	5 (8.9%)	3 (3.0%)	
Ethnicity			0.06
Not Hispanic Or Latino	46 (82.1%)	82 (81.2%)	
Hispanic Or Latino	5 (8.9%)	17 (16.8%)	
Unknown	5 (8.9%)	2 (2.0%)	
Sex			0.78
Female	27 (48.2%)	45 (44.6%)	
Male	29 (51.8%)	56 (55.4%)	
Smoking status (self-identified)			0.02
never smoked	17 (30.4%)	52 (51.5%)	
former smoker	5 (8.9%)	22 (21.8%)	
Smoker	2 (3.6%)	3 (3.0%)	
Unknown	20 (35.7%)	20 (19.8%)	
No data available	12 (21.4%)	4 (4.0%)	
BMI			0.24
Mean (SD)	28.1 (16.5)	30.9 (7.52)	
Median [Min, Max]	25.7 [13.7, 143]	30.4 [13.8, 56.9]	
Weighted Elixhauser score			0.62
Mean (SD)	12.9 (9.19)	12.1 (8.72)	
Median [Min, Max]	12.0 [0, 34.0]	12.0 [-4.00, 36.0]	
First MEWS score			0.09
Mean (SD)	2.38 (1.73)	1.91 (1.33)	
Median [Min, Max]	2.00 [1.00, 8.00]	1.00 [0, 7.00]	
Change in MEWS score			0.40
Mean (SD)	0.660 (1.41)	0.471 (1.21)	Mean (SD)
Median [Min, Max]	0.208 [-3.00, 5.00]	0.250 [-2.30, 5.50]	
Length of stay (days)			< 0.01
Mean (SD)	6.71 (4.10)	9.86 (7.20)	
Median [Min, Max]	6.00 [2.00, 20.0]	8.00 [2.00, 49.0]	
Severity at admission			0.85
Mild	49 (87.5%)	90 (89.1%)	
Moderate	3 (5.4%)	6 (5.9%)	
Severe	4 (7.1%)	5 (5.0%)	

^a Note: Receipt of HCQ could occur at any time during their hospital stay. Smoking status was indicated through point of contact queries; unknown status was an option for selection in this query. Change in MEWS score represents the difference in scores for a patient from the average available MEWS scores between 0–24 hours after admission and the average available MEWS scores between 36–60 hours after admission. Severity on admission was determined by the highest level of care required within 8 h of admission (mild = no ICU or mechanical ventilation; moderate = ICU but no mechanical ventilation; severe = required mechanical ventilation). Readmission data only includes those patients who were readmitted to a facility affiliated with the healthcare system in this analysis. P values represent test of means (two-sided t-test for continuous variables, chi square analysis for discrete variables).

mechanical ventilator support. Patients classified as “severe” disease required ventilator support, regardless of location.

Patient medication administration data were used to determine treatment groups. Patients were excluded if they had received any of the major COVID-19 investigational treatment medications other than HCQ. This included remdesivir, tocilizumab, siltuximab, sarilumab, leronlimab, and lopinavir/ritonavir.

Statistical analysis

Univariable analysis was conducted to determine patient demographic and clinical characteristics that had a statically significant effect on mortality for inclusion in the overall regression model. These variables (age, BMI, weighted Elixhauser score, severity on admission) were used to limit the population for analysis; patients with missing data in any of these variables were excluded from analysis. To account for cases of multiple comparisons, ANOVA with Tukey’s post-hoc test was used at a 0.05 significance level to evaluate statistical significance.

The primary outcome of interest was in-hospital mortality. Logistic regression was used to estimate the covariate-adjusted association between treatment with HCQ at any time and death. Covariates included in models were age, BMI, weighted Elixhauser score, receipt of AZM, first MEWS score and severity at admission (reference category = mild severity, never received HCQ). Prior to fitting the model, scatter plots and density plots were used to visually verify assumptions related to co-linearity and normality, respectively. Additionally, Cook’s D was used to measure the influence of potential outliers on the data. While no points were particularly influential, it was observed that one BMI measurement was recorded as 2,046.3 kg/m². Due to the unrealistic nature of this value, the median BMI of 29.55 kg/m² was imputed. All analyses were performed using R version 3.6.2.

Results

As of April 27, 2020, there were 1669 discharged patients with documented COVID-19 positive status (as determined by SARS-CoV-2 RT-PCR testing) and complete data for the variables of interest. We identified COVID-19 positive patients who had received either HCQ, with or without AZM, at any point in their admission and those who had no exposure to HCQ. Demographics for these patients by treatment group are presented in [Table 1](#).

Overall, there were few demographic differences between patients who were exposed to HCQ and those with no HCQ exposure. Patients who did not receive HCQ had a slightly higher weighted Elixhauser score, indicating more comorbidity severity within this group. Initial patient status, as indicated by the first MEWS score at admission, was equivalent between groups. Both groups were relatively stable within the first 48 h, as indicated by the change in MEWS score. The severity of patients at admission, determined by the highest level of care required within 8 h of admission was approximately the same between groups. When limited to those patients who died in the hospital, there were again few demographic differences between those that received HCQ and those with no HCQ exposure ([Table 2](#)). However, among patients who died, there was an observed difference in overall length of stay; this was longer, on average, among patients who had received HCQ ([Table 2](#)).

As our data set included patients who received HCQ at any point within their stay, there was the possibility that the treatment was a reflection of clinical prognoses or decline. We therefore explored various permutations of these groups with regard to clinical progression in order to control for this possible confounding. [Table 3](#) presents patient demographics outcomes segregated by severity at which patients in the HCQ exposure group received treatment. The majority of patients who received HCQ treatment

Table 3
Demographics and outcomes by severity at initiation of treatment.

	Received HCQ while at Mild severity (N=843)	Received HCQ while at Moderate severity (N=88)	Received HCQ while at Severe severity (N=42)
Age at admission			
Mean (SD)	59.7 (16.7)	62.2 (15.1)	64.5 (16.7)
Median [Min, Max]	60.0 [19.0, 103]	64.0 [29.0, 95.0]	70.0 [20.0, 89.0]
BMI			
Mean (SD)	33.4 (69.8)	31.4 (6.75)	32.5 (7.11)
Median [Min, Max]	29.9 [13.8, 2050]	30.2 [16.3, 50.8]	31.3 [20.0, 56.9]
Sex			
Female	397 (47.1%)	50 (56.8%)	17 (40.5%)
Male	446 (52.9%)	38 (43.2%)	25 (59.5%)
Weighted Elixhauser score			
Mean (SD)	5.27 (7.34)	7.14 (8.11)	9.60 (8.43)
Median [Min, Max]	5.00 [-10.0, 44.0]	5.00 [-7.00, 26.0]	7.50 [-4.00, 35.0]
Baseline MEWS score			
Mean (SD)	1.48 (1.01)	1.78 (1.37)	2.02 (1.26)
Median [Min, Max]	1.00 [0, 7.00]	1.00 [0, 7.00]	1.50 [1.00, 5.00]
Change in average MEWS 12–48 hours			
Mean (SD)	-0.0461 (0.786)	0.247 (1.32)	0.203 (1.26)
Median [Min, Max]	0 [-3.33, 4.00]	0 [-3.67, 5.50]	0.260 [-2.30, 4.33]
Length of stay (days)			
Mean (SD)	7.45 (4.94)	10.2 (6.51)	13.3 (8.73)
Median [Min, Max]	6.00 [1.00, 49.0]	9.00 [1.00, 28.0]	10.5 [1.00, 42.0]
HCQ days of therapy			
Mean (SD)	4.66 (1.85)	4.65 (1.69)	4.69 (2.38)
Median [Min, Max]	5.00 [1.00, 12.0]	5.00 [1.00, 11.0]	5.00 [1.00, 11.0]
Discharge disposition			
Expired	61 (7.2%)	19 (21.6%)	21 (50.0%)
Did not expire	782 (92.8%)	69 (78.4%)	21 (50.0%)

*Note: Severity was determined by the highest level of care at the time of drug administration (mild = no ICU or mechanical ventilation; moderate = ICU but no mechanical ventilation; severe = required mechanical ventilation). Change in MEWS score represents the difference in scores for a patient from the average available MEWS scores between 0–24 hours after admission (12-h score) and the average available MEWS scores between 36–60 hours after admission (48 h score).

had their first dose initiated while at mild severity (while receiving care on general medical/surgical ward). Patients who received treatment while at severe severity (on mechanical ventilation) tended to have higher baseline MEWS, higher weighted Elixhauser score, and more of these patients died.

The average time from admission to HCQ treatment was 38 h (Figure 1). Most (67%) patients received HCQ within 0–48 hours of admission; we did not see a significant decline in patient condition during this time, as measured by the change in MEWS score (Table 1). Overall, very few patients received treatment on the day of discharge (Figure 2). Of all the patients who received HCQ, 4% received treatment <24 h before discharge. There were 88 patients who received HCQ after admission to the ICU (with no mechanical ventilation) and 42 patients who received the treatment after being placed on mechanical ventilation. There was no apparent relationship between HCQ days of therapy and mortality rate when classified by patient severity at HCQ administration.

To account for the effect of patient demographics in the response to treatment and the risk of mortality, we created a multivariable regression model that included age at admission, BMI, sex, Elixhauser score, receipt of AZM, first MEWS score and severity at admission (Figure 3). In this model, we investigated whether HCQ treatment was associated with mortality. When accounting for all other variables, we found that the receipt of HCQ was associated with an 81% increase in the risk of the patient dying (OR: 1.81, 95% CI: 1.20–2.77, p = 0.01).

While the model above accounted for the administration of AZM, we performed additional analyses to determine if there was any potential interaction between HCQ and AZM in relation to patient mortality. In patients with no exposure to HCQ but with AZM exposure, mortality was 6% (30/472) while patients with no AZM or HCQ had a mortality of 12% (26/224) (p = 0.03). Mortality in patients with HCQ alone was 17% (14/82) and patients with both HCQ and AZM administration had a mortality of 10% (87/891) (p = 0.06). We performed an additional logistic regression with receipt of HCQ alone and the combination of HCQ and AZM as variables, and again observed increased risk of mortality with HCQ exposure (Figure 4).

Discussion

In this retrospective study, we found that treatment with HCQ had no benefit on mortality in COVID-19 patients. As provider preference largely dictated at what stage in disease progression HCQ was given, there was a wide range of treatment trajectories in

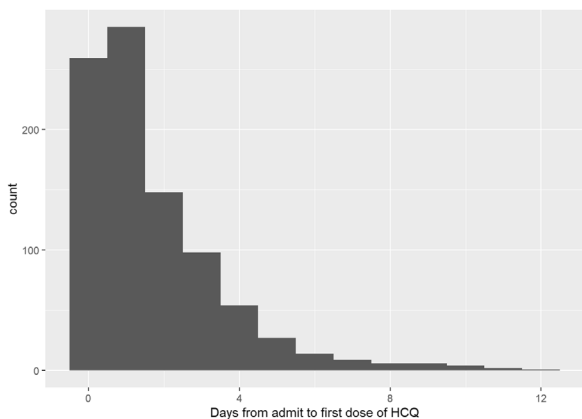


Figure 1. Days from admission to first dose of HCQ Patients represent those that received HCQ per definition. Days to first dose were calculated from the day of admission and the day of first documented administration of HCQ. Count represents the number of patients.

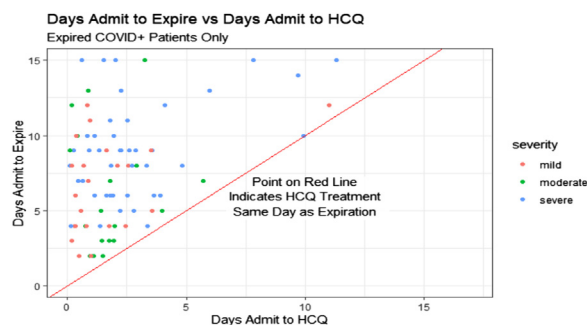


Figure 2. Relationship between days from admission to death versus days from admission to first HCQ administration. Data represent patients treated with HCQ who died. Time in days from admission to first administration of HCQ versus time from admission to death. Colors represent disease severity at the time of HCQ administration. Mild = no ICU or mechanical ventilation; moderate = ICU but no mechanical ventilation; severe = required mechanical ventilation.

our data set. When adjusting for patient characteristics and disease severity, we observed an increase in the risk of mortality associated with the receipt of HCQ.

In the absence of completed clinical trials, treatment protocols and dosing of HCQ have varied widely, which complicates comparison across different patient populations. While an optimal dose has not been established, early observational studies emphasized a loading dose followed by at least 4 days of treatment to reach a therapeutic level that could inhibit coronavirus replication (Colson et al., 2020; Perinel et al., 2020). However, subsequent studies have highlighted the potential cardiac effects, namely severe QT prolongation, associated with higher doses (Borba et al., 2020). Reflecting this uncertainty, the Infectious Diseases Society of America (IDSA) released guidelines on April 11, 2020 that included, among other recommendations, the recommendation that treatments for COVID-19, including chloroquine or HCQ, should only be used in the context of a clinical trial (Bhimraj et al., 2020). Since the release of these guidelines, many high-profile clinical trials have been suspended or altered, citing a lack of evidence of benefit of HCQ in interim analysis, and the US Food and Drug Administration has revised its guidance, including revoking the emergency use authorization for the use of hydroxychloroquine (Clinicaltrials.gov, 2020; Food and Drug Administration, 2020b; National Institute of Allergy and Infectious Diseases (NIAID), 2020; World Health Organization, 2020). Subsequent published trial results have confirmed a lack of effect of HCQ, alone or with AZM, on clinical outcomes (Cavalcanti et al., 2020).

The data from our retrospective study predate these latest guidelines and trial results, and thus we observed a spectrum of treatment timing in relation to patient admission and disease progression. While individual patient-level dosing information was not available at the time of this analysis, prescribers at participating facilities were affiliated with a large healthcare system and largely use similar formularies and general pharmacy guidelines for the dosing of HCQ in other disease states. We are reasonably certain that dosing regimens were in alignment with published guidelines at the time, namely an 800 mg loading dose followed by 400 mg per day for 4–7 days (Food and Drug Administration, 2020a). Thus, we were afforded the opportunity to investigate how HCQ treatment interacted with both patient characteristics and disease severity, and how this treatment could affect mortality outcomes. This is a question largely unanswered in the current COVID-19 research and could aid in the targeting of this treatment to those patients who have the potential to benefit with the lowest risk of adverse side effects.

Our analysis indicated that major risk factors for mortality among patients with COVID-19 include certain patient demographics and

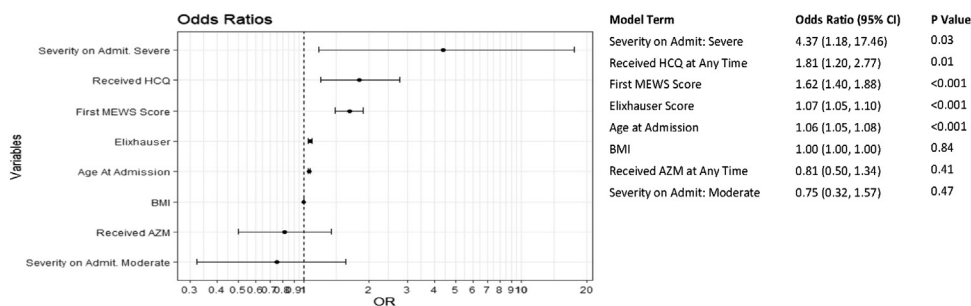


Figure 3. Risk of mortality in COVID-19 patients Multivariable logistic regression to estimate covariate-adjusted association between treatment with HCQ and death. Severity at admission refers to level of care required: mild = no ICU or mechanical ventilation; moderate = ICU but no mechanical ventilation; severe = required mechanical ventilation.

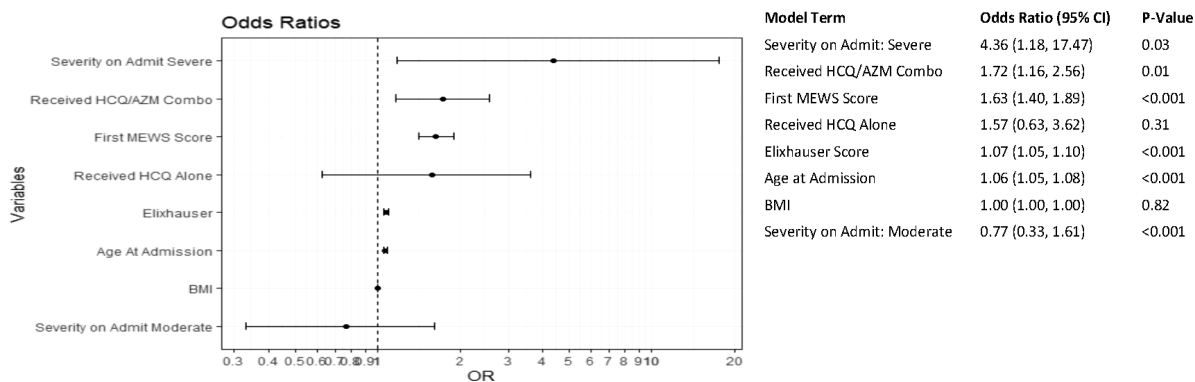


Figure 4. Risk of mortality in COVID-19 patients, HCQ + AZM combination Multivariable logistic regression to estimate covariate-adjusted association between treatment with HCQ + AZM and death. Severity at admission refers to level of care required: mild = no ICU or mechanical ventilation; moderate = ICU but no mechanical ventilation; severe = required mechanical ventilation.

clinical characteristics, regardless of treatment status. As other studies have shown, age is a major risk factor for mortality, with older patients at a substantial and significant risk of death (Li et al., 2020; Ruan et al., 2020; Zhou et al., 2020). Patients with more severe comorbidities, as estimated by weighted Elixhauser score, also have higher risk of mortality. Similarly, those patients who are admitted with higher initial MEWS scores or higher severity at admission have increased risk of death. However, taking these into account, we still observed a very substantial and significant detrimental effect of HCQ treatment on the risk of mortality. Our analysis, however, did not find a significant association of BMI, patient sex, or race with mortality, with or without HCQ, as has been reported in other studies (Chen et al., 2020; Richardson et al., 2020). This may be due to differences in the population between various countries and regions, and will require further investigation.

Overall, receipt of HCQ at any time during admission is associated with an increased mortality among all COVID-19 patients. While it is possible this could be due to patients with severe disease (requiring mechanical ventilation) receiving HCQ for the first time at this late stage in their disease progression, we found that this situation only applied to a small proportion of the population in our study. In addition, we observed that there may be some interaction between AZM and HCQ on the risk of mortality, although in patients receiving HCQ + AZM, we still observed an increase in the risk of mortality. At present, it is unclear if AZM was being prescribed to treat COVID-19 infection in general or for a specific purpose such as for treatment of pneumonia. If there is any benefit of AZM on mortality, our results suggest that administration of HCQ may diminish this effect.

One of the limitations of this study, like most real-world clinical trials, is that treatment with HCQ was not controlled. The determination of treatment was left entirely up to physician

discretion. Thus, a negative effect of a given treatment could be obtained if physicians only treated more severe patients with the medications, thus leading to an observed “no effect” of treatment due to the initial greater severity of the patients treated. This could be particularly true if the medications were being administered to patients with severe disease and who continued on a rapid downward progression. Conversely, if only patients with milder disease were being treated with the experimental medications, then a positive effect of the treatments might erroneously be observed.

In order to control for this potential confounding, we controlled for severity and MEWS scores at admission. Based on comparison of the MEWS scores for patients with and without HCQ treatment, there did not appear to be a bias in the patient populations which could readily account for the observed effects on mortality. If anything, the control group was slightly more impaired based on comorbidity scores, indicating that mortality would have been more likely to occur in this group versus the treatment group, which is opposite to our findings. Among patients who died, the initial MEWS score and weighted Elixhauser score tended to be higher among those that did not receive HCQ versus those that did receive the treatment. In addition, the consistent increase in mortality for the 3 COVID sub-groups, stratified by severity, supports the findings that these medications have a negative impact on patient outcomes.

In total, this retrospective analysis of the effect of HCQ and outcomes in COVID-19 patients found no benefit of HCQ treatment. When adjusted for patient characteristics and disease severity, this treatment was associated with an increased risk for mortality. These results emphasize the importance of controlled trials of COVID-19 treatment options and support recent recommendations against the use of this treatment in COVID-19 patients.

Conflict of interest

The authors declare no conflicts of interest.

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Ethical approval

This work was determined to be exempt from IRB oversight consistent with federal regulation and in accordance with institutional policy.

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