Original Research

The Effect of Hydroxychloroquine on In-Hospital Mortality in COVID-19

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Abstract

Background
Hydroxychloroquine (HCQ) is an antimalarial medication that has been tested against various viral illnesses. The available evidence regarding the role of HCQ in the coronavirus disease 2019 (COVID-19) remains controversial.

Methods
This is a comparative retrospective cohort study that aims to evaluate the efficacy and safety of HCQ in hospitalized patients with COVID-19. The primary outcome was all-cause in-hospital mortality. Secondary outcomes included ICU admission rate, mechanical ventilation, prolonged length of stay (LOS), QTc prolongation and cardiac arrest.

Results
A cohort of 175 hospitalized patients with COVID-19 were included with a median (interquartile range [IQR]) age of 66 [48–79] years. Of whom, 82 (47%) patients received HCQ.
The overall mortality rate was 34.1%; 95% CI [23.7–44.6] and 16.1%; 95% CI [8.5–23.7] in the HCQ group vs. the control group, respectively (p = 0.67). A Cox regression analysis was performed adjusting for age, gender, BMI, SpO2/FiO2 ratio and CXR findings, and demonstrated that the association between HCQ use and the all-cause in-hospital mortality was not statistically significant (HR = 1.15; 95% CI [0.54–2.48]; p-value = 0.72).
Patients who received HCQ were more likely to be admitted to the intensive care unit, require mechanical ventilation and have a prolonged LOS compared to those who did not receive the medication. No statistically significant difference was found in the likelihood of QTc prolongation or cardiac arrest.

Conclusions
The use of HCQ in patients hospitalized with COVID-19 confers no benefit in patient morbidity or mortality.

Keywords
coronavirus; COVID-19; SARS-CoV-2; pandemics; cohort studies; mortality; hospital mortality; survival; hydroxychloroquine, QTc interval; therapeutics

Introduction
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a contagious respiratory pathogen that originated in Wuhan, China, in December 2019. On January 21, 2020, the first case in the United States was confirmed by the Centers for Disease Control and Prevention (CDC).[1] The number of new cases and deaths has continued to exponentially increase all around the world raising the pressing need for effective therapeutic options.

Chloroquine (CQ) and Hydroxychloroquine (HCQ) sulfate are 4-aminoquinoline drugs

developed over 50 years ago and routinely used worldwide in management of malaria and various rheumatological diseases. In vitro studies suggested that these medications have antiviral activity against SARS-CoV-1, the Middle East respiratory syndrome (MERS), human and avian influenza and most recently, SARS-CoV-2.[2,3]

In consideration of the rapid spread of the COVID-19 pandemic and its significant morbidity and mortality, the FDA issued an Emergency Use Authorization (EUA) between March 28th and June 15th, 2020, for HCQ in the management of COVID-19. During this period, many studies have demonstrated conflicting data about the safety and efficacy of CQ and HCQ in patients with COVID-19. The use of these medications remains a matter of great controversy. The purpose of this study is to evaluate the safety and efficacy of HCQ in patients hospitalized with COVID-19.

Materials and Methods

This is a single-center retrospective cohort study of hospitalized patients diagnosed with COVID-19 from March 2020 to May 2020. Study approval was sought and obtained from the Institutional Review Board. Patient confidentiality was maintained at all times in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations.

Patients who were ≥ 18 years old and hospitalized for more than 24 hours with at least one positive polymerase chain reaction (PCR) for COVID-19 were included in the study. Demographic characteristics and clinical data were manually extracted from the electronic medical records system. Quick SOFA (qSOFA) and Charlson Comorbidity Index scores were calculated as previously described.[4,5] Patients with a body temperature of more than 38°C on admission were considered to have a fever. Radiographic findings on chest X-ray (CXR) were determined to be normal, mild, moderate or severe by a radiologist.

The primary endpoint was all-cause in-hospital mortality. Secondary outcomes included intensive care unit (ICU) admission rate, mechanical ventilation, prolonged length of stay (LOS) (more than seven days), corrected QT interval (QTc) prolongation and cardiac arrest. QTc > 500 millisecond or an increase of QTc > 60 milliseconds from baseline were considered to be prolonged.

Statistical analysis

We categorized the study participants into two groups based on HCQ administration during the hospitalization. Patients who received the standard of care without the use of HCQ were included in the control group. Continuous variables were reported as medians (interquartile ranges [IQR]), while categorical variables were reported as frequencies and percentages. In the comparative analysis, continuous and categorical variables were analyzed using Mann-Whitney U tests and chi-square tests; respectively.

Kaplan Meier test was utilized to estimate the crude survival time and the unadjusted statistical difference between groups. A Cox proportional hazards model was conducted for time to death in both groups to estimate the hazard ratio after adjusting for the age, gender, body mass index (BMI) and characteristic variables with a statistically significant difference between the two study groups.

Bivariate and multivariate logistic regression analyses were used to investigate the association between HCQ treatment and the secondary outcomes before and after adjusting for confounding factors. All tests were two-tailed, and a p-value of < 0.05 was considered statistically significant. Statistical analysis was performed using JMP statistical software version 13 (SAS Institute, Cary, NC) and IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA).

Results

The cohort included 175 patients with a median (interquartile range [IQR]) age of 66 (48–79) years. Eighty-two of these patients (47%) received HCQ during the hospitalization period and were included in the HCQ group. Seventy-two patients (88%) of the HCQ group, received azithromycin in addition to HCQ. The median [IQR] for the length of treatment with HCQ was 5 [3–6] days, and the median and [IQR] for the time of initiation of treatment was 2 [2–4] days from admission. Patients

Table 1. Demographics and baseline characteristics of the study population.

	Total (n=175)		
Demographic characteristics	**Hydroxychloroquine (n=82)**	**No Hydroxychloroquine (n=93)**	**P value**
Age	66 (50-77)	63 (45-80)	0.12
Male gender	47 (57%)	50 (54%)	0.64
Race			0.81
Caucasian	48 (61%)	59 (65%)	
African American	14 (18%)	14 (16%)	
Other	17 (22%)	17 (19%)	
Ethnicity			0.73
Hispanic	22 (28%)	23 (25%)	
Non-Hispanic	57 (72%)	68 (75%)	
BMI	28.3 (24.3-32.7)	27.7 (24.6-31.2)	<0.01*
Smoking	8 (10%)	3 (3%)	0.07
Charlson Comorbidity Index	3 (1-5)	3 (0.5-4)	0.41
Myocardial infarction	10 (12%)	10 (11%)	0.76
CHF	5 (6%)	7 (8%)	0.71
PVD	3 (4%)	1 (1%)	0.25
Stroke/TIA	5 (8%)	2 (2%)	0.18
Dementia	11 (13%)	16 (17%)	0.78
COPD	2 (2%)	5 (5%)	0.31
CTD	5 (6%)	0 (0%)	0.02*
Peptic ulcer disease	1 (1%)	0 (0%)	0.45
Liver disease	0 (0%)	0 (0%)	0.93
Diabetes	25 (31%)	23 (25%)	0.39
Hemiplegia	0 (0%)	0 (0%)	0.75
CKD	4 (5%)	4 (4%)	0.85
Localized tumor	2 (2%)	7 (7%)	0.27
Metastatic tumor	6 (7%)	1 (1%)	0.50
Leukemia	0 (0%)	1 (0%)	0.75
Lymphoma	0 (0%)	1 (1%)	0.50
AIDS	0 (0%)	0 (0%)	0.75
qSOFA score ≥ 1	23 (28%)	21 (23%)	0.56
Respiratory rate >22	15 (19%)	6 (7%)	0.02*
SBP < 100 mmHg	2 (3%)	5 (6%)	0.31
Altered mental status	7 (9%)	12 (13%)	0.34
SpO2/FiO2 ratio	4.2 (2.9-4.6)	4.6 (4.0-4.7)	<0.01*
Fever >38.0 °C	21 (26%)	14 (16%)	0.09
Abnormal CXR findings	65 (79%)	51 (55%)	0.01*
Mild	37 (64%)	29 (38%)	
Moderate	4 (5%)	12 (16%)	
Severe	24 (31%)	10 (13%)	
Steroids use	15 (20%)	6 (7%)	0.02*
Azithromycin use	72 (88%)	60 (65%)	<0.01*

Variables are reported as frequency and percentages (%) or median and interquartile range (IQR).

Abbreviation: BMI; body mass index, CHF; congestive heart failure, PVD; peripheral vascular disease, TIA; transient ischemic attack, COPD; chronic obstructive pulmonary disease, CTD; connective tissue disease, CKD; chronic kidney disease, AIDS; acquired immunodeficiency syndrome, SBP; systolic blood pressure, SpO2/FiO2; peripheral blood oxygen saturation/fraction of inspired oxygen, CXR; plain chest radiography.

*P values < 0.05

who received HCQ were more likely to have a higher BMI, connective tissue disorders, a lower peripheral blood oxygen saturation/fraction of inspired oxygen (SpO2/FiO2) ratio and abnormal CXR findings. (**Table 1**)

Primary outcome

The overall all-cause in-hospital mortality was 24.6%; 95% CI [18.1–31.0] in the total study population, 34.1%; 95% CI [23.7–44.6] in the HCQ and 16.1%; 95% CI [8.5–23.7] in the control group. In a bivariate analysis, there was not a statistical significant change in survival rate over time in the HCQ group compare to the control group (27.6 days; 95% CI [22.2–33.1] and 25.8 days; 95% CI [20.9–30.7] in the HCQ vs. the control group, respectively); p = 0.67.
In the adjusted Cox regression model, the association between HCQ use and all-cause in-hospital mortality was not statistically significant (HR = 1.15; 95% CI [0.54–2.48]; p-value = 0.72). This model was adjusted for age, gender, BMI, SpO2/FiO2 ratio and CXR findings. (**Figure 1**)

Secondary outcomes

Patients who received HCQ were more likely to have a prolonged LOS with a median [IQR] of 9 [5–19] days, compared to 6 [3–10] days in the control group (p < 0.01). Additionally, the HCQ group was more likely to be admitted to the ICU, require mechanical ventilation or have a prolonged LOS. No significant association was observed between HCQ use and the incidence of QTc prolongation or cardiac arrest. The increased likelihood of ICU admission, mechanical ventilation and prolonged LOS in the HCQ group remained statistically significant in the multivariate analysis after adjusting for age, gender, BMI, SpO2/FiO2 ratio and CXR findings. (**Table 2**)

Discussion

The role of HCQ in the management of patients with COVID-19 is controversial. Recent in-vitro evidence and anecdotal clinical data have suggested a potential benefit for the use of HCQ in patients with COVID-19.[6-8] However, the early literature should be interpreted with caution due to the lack of a control group.
In our comparative study, we adjusted for possible confounders and found no mortality benefit for the use of HCQ in hospitalized patients with COVID-19 compared to the standard of care.

Our results support findings from previous observational studies.[9-11] One large, single-center, study conducted in hospitalized patients with COVID-19 found no association between receiving HCQ and mortality rate.[9] Another multicenter cohort study by Rosenberg et al. showed no mortality benefit

Table 2. In-hospital clinical outcomes and their difference in between the study groups.

	Total (n=175)			
Clinical outcomes	**Hydroxychloroquine (n=82)**	**No Hydroxychloroquine (n=93)**	**P value[a]**	**P value[b]**
ICU admission	34 (41%)	2 (2%)	<0.01*	<0.01*
Mechanical ventilation	16 (20%)	3 (3%)	<0.01*	0.03*
Prolonged LOS	50 (60%)	36 (39%)	<0.01*	<0.01*
QTc prolongation	16 (29%)	6 (19%)	0.16	0.10
Cardiac arrest	5 (6%)	1 (1%)	0.06	0.32

Outcomes are reported as frequency and percentages.

Chi-square test was performed to estimate the statistical significance in difference between groups.

[a] Unadjusted bivariate analysis. [b] Multivariate analysis adjusted for age, gender, body mass index, peripheral blood oxygen saturation/fraction of inspired oxygen (SpO2/FiO2) ratio and the severity of radiographic findings on chest X-ray.

ICU; intensive care unit, LOS; length of stay, QTc; corrected QT interval.

*P values < 0.05.

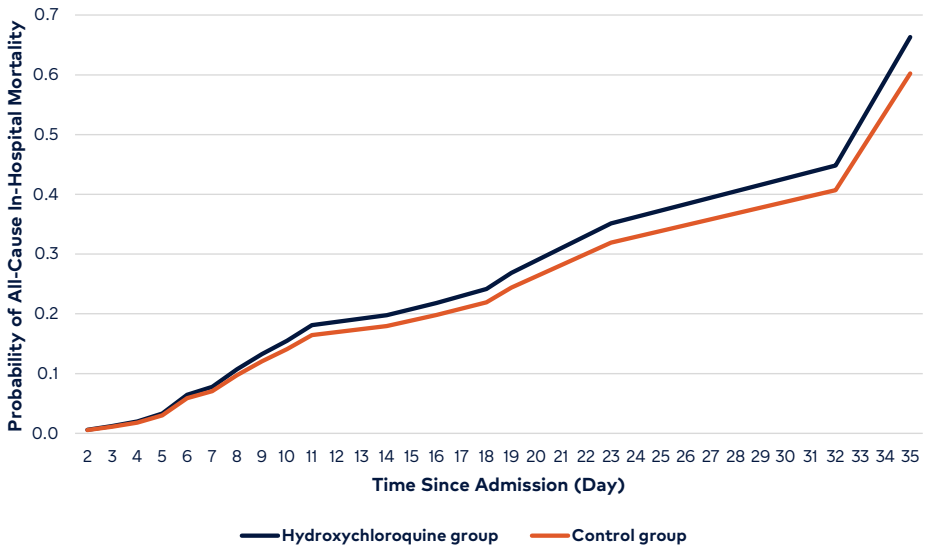

Figure 1. Cox proportional hazards model of in-hospital mortality.

for the use of HCQ.[10] A retrospective study by Magagnoli et al. found a higher risk of death in patients treated with HCQ compared to those who did not receive the medication.[12]

Conversely, a retrospective observational study conducted at the Henry Ford Health System observed a statistically significant association between the use of HCQ, with or without azithromycin, and a higher survival rate among hospitalized patients with COVID-19.[13] The majority of the patients who received HCQ also received corticosteroids with a statistically significant difference between groups. Thus, these results should be interpreted with caution in light of the recent evidence showing a clinical benefit for the use of dexamethasone in hospitalized patients with COVID-19 in lowering the 28-day mortality rate by 17% with a 95% CI ranging between 7% and 25%.[14]

Our study found that patients in the HCQ group were more likely to have a prolonged LOS. Similar trends were noted in a randomized clinical trial of 30 treatment-naïve patients with COVID-19 in China where Chen et al. demonstrated that patients who were treated with HCQ had a longer hospital stay than the control group.[15] Our study also noted that patients in the HCQ group were more likely to require escalation of care leading to admission to the intensive care unit and mechanical ventilation. On the contrary, Magagnoli et al. found no association between HCQ use, with or without azithromycin, and the risk of intubation when compared to those who did not receive the medication.[12]

In our study, patients treated with HCQ had a higher incidence of QTc prolongation, although the association was not statistically significant. Similarly, a large multinational registry showed an increased risk of ventricular arrhythmias in patients treated with HCQ (6.1% compared to 0.3% in controls) without evidence of an added clinical benefit.[16] The risk of ventricular arrhythmias can be explained by the effect of HCQ on prolonging the QTc interval, particularly when co-administered with a macrolide. Two cohort studies of hospitalized patients with COVID-19 observed an increased likelihood of QTc prolongation in patients treated with HCQ. This risk was higher in those who additionally received azithromycin.[17,18] Additionally, a randomized controlled trial enrolled 150 patients to either HCQ or standard of care found an increased likelihood of adverse event in the HCQ group (30% compared to 9% in the standard care group).[19]

The available evidence to date against the use of HCQ in patients with COVID-19 outweighs the available supportive evidence. Two recent randomized, double-blinded, placebo-controlled trials demonstrated the lack of efficacy of HCQ when used as prophylaxis or early therapy against COVID-19.[20,21] However, both

trials lacked a consistent proof of exposure to SARS-CoV-2.

Limitations

Due to its retrospective and observational nature, our study methodology prevents drawing a causation relation. Moreover, the lack of randomization introduces a risk of confounding bias. Patients treated with HCQ in our cohort were more likely to be sicker at baseline than those who did not receive the medication. This can potentially blunt the estimated effect of HCQ on the tested clinical outcomes. In an attempt to control for the aforementioned limitations, an adjusted multivariable regression was performed.

Conclusion

Our study did not find any mortality benefit from the use of HCQ in patients hospitalized with COVID-19. In light of the paucity of evidence in support of the benefits of chloroquine analogs in the management of COVID-19 and its potential adverse effects, we recommend restricting the use of Hydroxychloroquine to clinical trials until more definitive evidence from ongoing randomized clinical trials (RCTs) aimed to assess the efficacy of HCQ in COVID-19 becomes available.

Conflicts of Interest

The authors declare they have no conflicts of interest.

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References

1. Holshue ML, DeBolt C, Lindquist S, et al. First Case of 2019 Novel Coronavirus in the United States. *N Engl J Med*. 2020;382(10):929-936. https://doi.org/10.1056/nejmoa2001191
2. Al-Bari MAA. Targeting endosomal acidification by chloroquine analogs as a promising strategy for the treatment of emerging viral diseases. *Pharmacol Res Perspect*. 2017;5(1):e00293. https://doi.org/10.1002/prp2.293
3. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269-271. https://doi.org/10.1038/s41422-020-0282-0
4. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676-682. https://doi.org/10.1093/aje/kwq433
5. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):762-774. https://doi.org/10.1001/jama.2016.0288
6. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov*. 2020;6:16. Published 2020 Mar 18. https://doi.org/10.1038/s41421-020-0156-0
7. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. *Travel Med Infect Dis*. 2020;34:101663. https://doi.org/10.1016/j.tmaid.2020.101663
8. Million M, Lagier JC, Gautret P, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. *Travel Med Infect Dis*. 2020;35:101738. https://doi.org/10.1016/j.tmaid.2020.101738
9. Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med*. 2020;382(25):2411-2418. https://doi.org/10.1056/nejmoa2012410
10. Rosenberg ES, Dufort EM, Udo T, et al. Association of Treatment with Hydroxychloroquine or Azithromycin with In-Hospital Mortality in Pa-

tients With COVID-19 in New York State. *JAMA*. 2020;323(24):2493-2502. https://doi.org/10.1001/jama.2020.8630

11. Mahévas 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 [published correction appears in *BMJ*. 2020 Jun 18;369:m2328]. *BMJ*. 2020;369:m1844. Published 2020 May 14. https://doi.org/10.1136/bmj.m1844
12. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. Preprint. *medRxiv*. 2020;2020.04.16.20065920. Published 2020 Apr 21. https://doi.org/10.1101/2020.04.16.20065920
13. Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *Int J Infect Dis*. 2020;97:396-403. https://doi.org/10.1016/j.ijid.2020.06.099
14. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19: Preliminary Report [published online ahead of print, 2020 Jul 17]. *N Engl J Med*. 2020;NEJMoa2021436. https://doi.org/10.1056/nejmoa2021436
15. Chen J, Liu D, Liu L, et al. [A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19.] *Zhejiang Da Xue Xue Bao Yi Xue Ban*. 2020;49(2):215-219. https://doi.org/10.3785/j.issn.1008-9292.2020.03.03
16. Mehra MR, Ruschitzka F, Patel AN. Retraction: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis [retraction of: *Lancet*. 2020 May 22;:]. *Lancet*. 2020;395(10240):1820. https://doi.org/10.1016/s0140-6736(20)31324-6
17. Mercuro NJ, Yen CF, Shim DJ, et al. Risk of QT Interval Prolongation Associated with Use of Hydroxychloroquine with or without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(9):1036-1041. https://doi.org/10.1001/jamacardio.2020.1834
18. Bessière F, Roccia H, Delinière A, et al. Assessment of QT Intervals in a Case Series of Patients with Coronavirus Disease 2019 (COVID-19) Infection Treated with Hydroxychloroquine Alone or in Combination with Azithromycin in an Intensive Care Unit. *JAMA Cardiol*. 2020;5(9):1067-1069. https://doi.org/10.1001/jamacardio.2020.1787
19. 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. Published 2020 May 14. https://doi.org/10.1136/bmj.m1849
20. 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(6):517-525. https://doi.org/10.1056/nejmoa2016638
21. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19: A Randomized Trial. *Ann Intern Med*. 2020;173(8):623-631. https://doi.org/10.7326/m20-4207