Impact of hydroxychloroquine on disease progression and ICU admissions in patients with SARS-CoV-2 infection

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Purpose. To evaluate whether use of hydroxychloroquine was associated with a reduced likelihood of intensive care unit (ICU) admission in patients with coronavirus disease 2019 (COVID-19) in the early weeks of the pandemic.

Methods. A retrospective, observational cohort study was conducted to determine selected treatment outcomes in 336 patients hospitalized with COVID-19 at an acute care community hospital in the Hudson Valley region of New York from March 20 to April 20, 2020. Eligibility included admission to the hospital, a laboratory-confirmed diagnosis of SARS-CoV-2 infection, and no need for intubation or intensive care at admission. The median (interquartile range) ages of patients who received hydroxychloroquine (n = 188) and those who did not (n = 148) were 68 (58-82) and 64 (51-73) years, respectively. In a multivariable model that included age, gender, obesity, diabetes, and hydroxychloroquine use, patients who received hydroxychloroquine were significantly more likely than those not treated with the drug to be transferred to an ICU (odds ratio, [OR], 8.1; 95% confidence interval [CI]: 3.8-17) and significantly more likely to be intubated (OR, 7.99; 95% CI, 3.76-16.91); these associations were not influenced by disease severity. In-hospital mortality did not differ significantly with disease severity between those who did and those who did not receive hydroxychloroquine.

Conclusion. Hydroxychloroquine use was significantly associated with increased risks of ICU admission and intubation in patients with mild, moderate, and severe symptoms of COVID-19. There were no significant between-group differences in mortality with use vs nonuse of hydroxychloroquine.

Keywords: coronavirus, hydroxychloroquine, infection

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Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) has been characterized as a global pandemic, with a current case-fatality rate of 2.2% in the United States alone.[1] In New York State, COVID-19 had resulted in over 33,000 deaths as of November 17, 2020—the largest COVID-19 mortality burden in the nation.[2] The illness course has been variable and unpredictable, as many patients infected with SARS-CoV-2 remain asymptomatic or have mild symptoms, while others progress to developing severe pneumonia requiring mechanical ventilation. Therapeutic agents under investigation target different phases of COVID-19, including acute viral illness and pulmonary and proinflammatory phases. Due to the rapid spread and progression of COVID-19, effective treatments are desperately needed.

Numerous medications, including hydroxychloroquine, have been used to treat COVID-19 because of their antiviral and anti-inflammatory properties.

In vitro studies of SARS-CoV-2 suggested a possible antiviral effect of hydroxychloroquine due to its ability to elevate endosomal pH, disrupt intracellular transport of the virus, and alter glycosylation of angiotensin-converting enzyme 2 (ACE-2), thereby preventing viral entry to ACE-2.[3] Despite the widespread off-label use of hydroxychloroquine in the treatment of COVID-19, it has not been proven to be effective. Initial results from preliminary small studies have been inconclusive; therefore, during the initial surge of COVID-19 cases in April 2020, the Infectious Diseases Society of America (IDSA) recommended that hydroxychloroquine, with or without azithromycin, should only be used in the context of a clinical trial.[4]

Hydroxychloroquine has been demonstrated to have a vast array of mechanisms, including immunomodulatory, antithrombotic, antiviral, hypoglycemic, and even antineoplastic effects. However, it has also been associated with significant toxicities, including cardiac arrhythmias and irreversible retinal damage.[5-8] Emerging data and anecdotal observations suggest a limited benefit of hydroxychloroquine in slowing or preventing progression of COVID-19. Therefore, we aimed to determine the association of hydroxychloroquine and its value in preventing admission to an intensive care unit (ICU), intubation, and mortality in patients with COVID-19.

Methods

Study design. A retrospective, observational cohort study was conducted to determine the impact of hydroxychloroquine on disease progression in patients with COVID-19. The study was approved by the institutional review board of Montefiore Nyack Hospital and was granted a waiver of patient consent requirements. The cohorts included patients who received hydroxychloroquine and those who did not. The primary outcome was ICU admission. Secondary outcomes included need for intubation and in-hospital mortality.

KEY POINTS

- A retrospective cohort study was conducted to determine whether hydroxychloroquine use was associated with disease progression among hospitalized patients with coronavirus disease 2019 (COVID-19).

- Use of hydroxychloroquine was associated with higher rates of ICU admission and intubation in patients with COVID-19 regardless of symptom severity.

- Due to the lack of published data from randomized controlled trials during the initial pandemic surge, real-time data collection and analysis was essential for identifying trends and adapting COVID-19 treatment protocols accordingly.

Patients who received hydroxychloroquine initially received a 5-day course of therapy that included a loading dose of 400 mg every 12 hours on day 1 followed by a dose of 200 mg every 12 hours on days 2 through 5.[9] Approximately halfway through our study period, this regimen was updated based on pharmacokinetic evidence and Monte Carlo simulations that suggested the need for a higher loading dose followed by a shorter course of therapy. The new regimen included a one-time 800-mg loading dose followed by doses of 400 mg at 6, 24, and 48 hours afterwards.[10,11] The 5-day course of therapy was not used in any patients once the 2-day course was initiated. Patients were defined as having received hydroxychloroquine if they were receiving it at study baseline or received it during hospital admission prior to intubation.

The decision to use hydroxychloroquine was often based on patient-specific clinical factors such as oxygen saturation level. Therefore, we tested

the relationship between covariates (ie, disease severity, age, gender, obesity, and diabetes) using χ^2 tests and identified disease severity as the only variable that was significantly correlated with hydroxychloroquine use, with a moderate to strong positive relationship (phi coefficient, 0.39). We controlled for this collinearity with a secondary analysis of the data by matching the study population by disease severity (mild or moderate symptoms vs severe symptoms) and reanalyzed each treatment cohort.

Patient identification. Consecutive patients admitted with a diagnosis of COVID-19 from March 20 to April 20, 2020, were included. Three patients who had been in the hospital since November 2019 and contracted COVID-19 during this time period were included as well. Patients were identified by International Classification of Diseases, 10th revision (ICD-10) codes and by laboratory results that were positive for COVID-19 and reported in our electronic health record (EHR). Information on patients with a positive COVID-19 test was pulled into a data mining system when they were identified in our EHR, which allowed us to pull a report on all the patients.

Patients were tested according to Centers for Disease Control and Prevention (CDC)–recommended procedures, which included a deep nasopharyngeal swab followed by viral RNA detection by reverse transcriptase polymerase chain reaction assay. Patients were included in the cohorts if they were admitted during the study time frame and tested positive for SARS-CoV-2. Disease severity was determined according to EHR documentation at the time of hydroxychloroquine initiation or, for patients who did not receive it, at admission. Patients were classified as having mild disease if they had a fever and cough, with or without diarrhea. Moderate disease severity was defined as mild symptoms in addition to shortness of breath along with an oxygen saturation greater than 93% on room air. Severe disease was defined as fever, cough, shortness of breath along with

an oxygen saturation of ≤93% on room air, and a requirement of supplemental oxygen. Patients were excluded if they did not test positive for SARS-CoV-2, if they required intubation within 24 hours of admission, or if they were not admitted to the hospital.

Data abstraction. All patients who had a positive test for SARS-CoV-2 were captured in our data mining system and their records subsequently analyzed for various factors, including age, gender, height, and weight; factors related to disease severity, as described above; history of diabetes mellitus; change in oxygen supplementation status; whether the patient decompensated during the admission and required intubation; ICU admission, ICU length of stay (LOS), and total hospital LOS; and discharge disposition. All data were manually abstracted from the EHR and stored in a spreadsheet that was saved on a private, internal server maintained by the hospital. All protected health information was censored during data collection.

Statistical analysis. We calculated that a sample size of 106 patients in each arm was needed in order to detect an 18% difference in ICU admission rates between the arms with a power of 80% and an α of 0.05. These calculations were based on internal data that showed ICU admission rates to be 59% and 41% overall in populations of patients who received hydroxychloroquine and those who did not, respectively. In order to control for multicollinearity, we reanalyzed the data after matching for disease severity. We recalculated sample sizes based on ICU admission rates within the groups of patients with mild to moderate or severe disease. We determined that the mild to moderate disease group should have 32 patients in each arm in order to achieve 80% power with an α of 0.05, and the severe group should have 33 patients in each arm to achieve 90% power with an α of 0.01.[12]

We set the primary and secondary outcomes as categorical dependent variables and hydroxychloroquine use as the categorical independent variable.

We then calculated significance and correlation coefficients using a binomial model that included the independent variable (hydroxychloroquine use) and the age, gender, obesity, and diabetes covariates using a multivariable logistic regression technique. Pseudo R^2 values were derived from the Nagelkerke index. We calculated significance levels for discrete and continuous demographic values within and between the cohorts using χ^2 and Student t tests. We also calculated the odds ratio (OR) and 95% confidence interval (CI) for reaching one of the outcomes according to whether a patient received hydroxychloroquine in the separate disease state analyses. LOS was evaluated with a Kaplan-Meier plot, with censoring of data on patients who expired. A log rank test was used to evaluate treatment cohorts. Statistical analyses were done using IBM SPSS Statistics, Version 27.0 (IBM Corporation, Armonk, NY).

Results

Population characteristics. A total of 336 consecutive patients admitted with COVID-19 were included in the study. A total of 188 patients (56%) received hydroxychloroquine and 148 (44%) did not receive hydroxychloroquine. All patients included were COVID-19 positive, and 19 patients without a positive laboratory confirmation were excluded. Out of the patients who received hydroxychloroquine, 153 patients received treatment during the first 24 hours of admission and 35 patients were treated after the first day of their hospital stay.

The per-group baseline characteristics are summarized in Table 1. Baseline characteristics show an overall mean (SD) age of 64.3 (17.0) years and a predominance of men (n = 209 [62.2%]). Most patients (71.7%) were obese, and 94 patients (28%) of the overall cohort also had diabetes.

Effect of hydroxychloroquine on ICU admission rates. There were 76 patients (22.6%) who were admitted to the ICU. Significantly more

patients who received vs did not receive hydroxychloroquine were admitted to the ICU (35.6% vs 6.1%, P < 0.0001; Figure 1A). A logistic regression was performed to ascertain the effects of age, gender, obesity, diabetes, and hydroxychloroquine use on the likelihood that a patient's condition would worsen and require a transfer to an ICU setting. The results of logistic regression modeling were statistically significant ($\chi^2(5)$ = 45.787, P < 0.05). The model explained 19.7% (Nagelkerke R^2) of the variance in ICU transfers and correctly classified 76.9% of cases. Patients who received hydroxychloroquine were 8.05 (95% CI, 3.8-17.0) times more likely to have been transferred to an ICU than those who did not receive it. Other covariates in the model were not significantly associated with an ICU transfer, and these effects were not influenced by severity of symptoms at the time hydroxychloroquine therapy was started (Table 2).

Effect of hydroxychloroquine on intubation and LOS and mortality rates. There were 73 patients (21.7%) who required intubation. The use vs nonuse of hydroxychloroquine was significantly associated with a higher rate of intubation (34.0% vs 6.1%, P < 0.0001; Figure 2A), and the multivariable model showed a corresponding significantly greater intubation risk (OR, 7.99; 95% CI, 3.76-16.91). Hydroxychloroquine use was consistently associated with a significantly greater risk of intubation when patients were analyzed according to their disease state. When patients were grouped by disease severity, obesity was associated with a significantly higher risk of intubation in those with mild to moderate disease (OR, 4.41; 95% CI, 1.01-19.28). Other covariates in the model were not significantly associated with intubation, and these effects were not influenced by severity of symptoms at the time of hydroxychloroquine initiation (Table 3).

There was no significant difference in overall LOS values between the treatment cohorts when accounting for mortality (P = 0.193; Figure 3). Additionally,

Table 1. Baseline Patient Demographics Overall and by Study Cohort[a]

Characteristic	Overall (*n* = 336)	HCQ Use (*n* = 148)	No HCQ Use (*n* = 188)
Age, mean (SD), y	64.3 (17.0)	67.3 (17.8)	62 (15.9)
Age range, y			
18–40	35 (10.4)	14 (9.5)	21 (11.2)
41–60	91 (27.0)	36 (24.3)	55 (29.3)
61–80	147 (43.8)	58 (39.2)	89 (47.3)
>81	63 (18.8)	40 (27.0)	23 (12.2)
Male	209 (62.2)	84 (56.8)	125 (66.5)
Diabetes	94 (28.0)	42 (28.4)	52 (27.7)
Obesity (all types)	241 (71.7)	94 (63.5)	141 (75.0)
Overweight	118 (49.0)	56 (59.6)	62 (44.0)
Obesity class I	62 (25.7)	21 (22.3)	41 (29.0)
Obesity class II	31 (12.9)	8 (8.5)	23 (16.3)
Obesity class III	24 (10.0)	9 (9.6)	15 (10.6)

Abbreviations: HCQ, hydroxychloroquine; SD, standard deviation.
[a]All data are number and percentage of patients unless otherwise indicated.

in-hospital mortality was similar among those who received and those who did not receive hydroxychloroquine (29.8% vs 25.0%, *P* < 0.603), and when analyzed by disease severity, the only factor that significantly increased the odds of mortality was age; older patients with mild to moderate disease and those with severe disease were 1.1 (95% CI, 1.04-1.06) and 1.04 (95% CI, 1.02-1.06) times more likely than younger patients to expire, respectively. The mean ages of patients with mild to moderate and patients with severe disease who expired were 78.2 years and 70.1 years, respectively, and patients in each of these subgroups were significantly older on average than those who did not expire (mean ages of 63.6 and 62.1 years, respectively; *P* < 0.01 for both comparisons).

Analysis by disease severity at hydroxychloroquine initiation or admission. Collinearity between hydroxychloroquine use and disease severity was controlled for by matching all patients by disease severity and analyzing for the influence of hydroxychloroquine on the various outcomes. There were 122 patients (36.3%) with mild to moderate disease and 214 (63.7%) with severe disease. For the group with

mild to moderate disease overall, the mean (SD) age was 62.6 (19.3) years (mean age, 64 years vs 60 years in the hydroxychloroquine vs no treatment cohorts, *P* = 0.29); males made up 57.4% of the group, 37.5% had a body mass index (BMI) that categorized them as obese, and 24.6% had diabetes. For the severe disease group, the mean (SD) age was 65.1 (15.4) years; however, patients who received hydroxychloroquine were significantly younger than those who did not, on average (62.4 years vs 71.7 years, *P* < 0.01). Males made up 65.0% of the severe disease group, 34.3% had a BMI that categorized them as obese, and 30.0% had diabetes.

In the mild to moderate disease group, 37 patients (30.3%) and 85 patients (69.7%) received and did not receive hydroxychloroquine, respectively; in the severe disease group, there were 151 patients (70.6%) and 63 patients (29.4%), respectively. In our multivariable model, we found that patients with mild to moderate disease were more likely to have been admitted to an ICU if they received hydroxychloroquine (24.3% vs 2.4%, *P* < 0.003; Figure 1B). Similarly, we saw that patients with severe disease

were also more likely to have been admitted to an ICU if they received hydroxychloroquine (38.4% vs 11.1%, *P* = 0.001; Figure 1C).

There was a similar trend when the need for intubation was analyzed according to disease severity. Patients with mild to moderate disease were at a higher risk for intubation if they received hydroxychloroquine (27.0% vs 3.5%, *P* < 0.001; Figure 2B). We observed that patients with severe disease were also at a higher risk for intubation if they received hydroxychloroquine (35.8% vs 9.5%, *P* = 0.001; Figure 2C).

Discussion

Hydroxychloroquine gained attraction as a possible therapeutic agent for use against COVID-19 due to a single in vitro study that demonstrated higher potency of hydroxychloroquine relative to chloroquine.[9] These results were extrapolated to support wide-scale use of the drug in patients with COVID-19. In our analysis, hydroxychloroquine use was associated with significantly increased risks of ICU admission and intubation after adjusting for initial disease severity. We did not see a significant difference in overall in-hospital

mortality among groups, which was consistent with previous observational studies done in New York.[13,14] Our findings suggest that the possible benefit of hydroxychloroquine against COVID-19 observed in vitro does not translate into beneficial clinical outcomes and use of the drug was associated with worsening of the disease.

The largest pertinent randomized controlled trial to date, which included 479 hospitalized adults who received hydroxychloroquine, was stopped early due to a lack of efficacy compared to placebo use at day 14 after randomization.[15] One smaller randomized controlled trial evaluated the effectiveness of hydroxychloroquine in 150 patients with COVID-19 and found no benefit in terms of conversion to SARS-CoV-2–negative status or symptom alleviation relative to standard-of-care measures after 28 days.[16] Chen et al[17] conducted another smaller randomized controlled trial involving 62 patients with COVID-19 and observed a 1-day difference in time to alleviation of cough and fever in the hydroxychloroquine group. Although these were prospective randomized controlled trials, the benefits observed with hydroxychloroquine use for COVID-19 were minimal.

A large retrospective analysis of data from hospitalized patients with confirmed COVID-19 among the Veterans Affairs population concluded that the use vs nonuse of hydroxychloroquine was associated with 2-fold higher mortality; however, symptom severity upon hydroxychloroquine initiation was not measured.[18] The study investigators also did not disclose the hydroxychloroquine doses used or durations of therapy. In contrast, we sought to eliminate these potential confounders in our study by creating 2 separate cohorts: patients with mild

Figure 1. Association of hydroxychloroquine use with intensive care unit (ICU) admission, by disease severity.
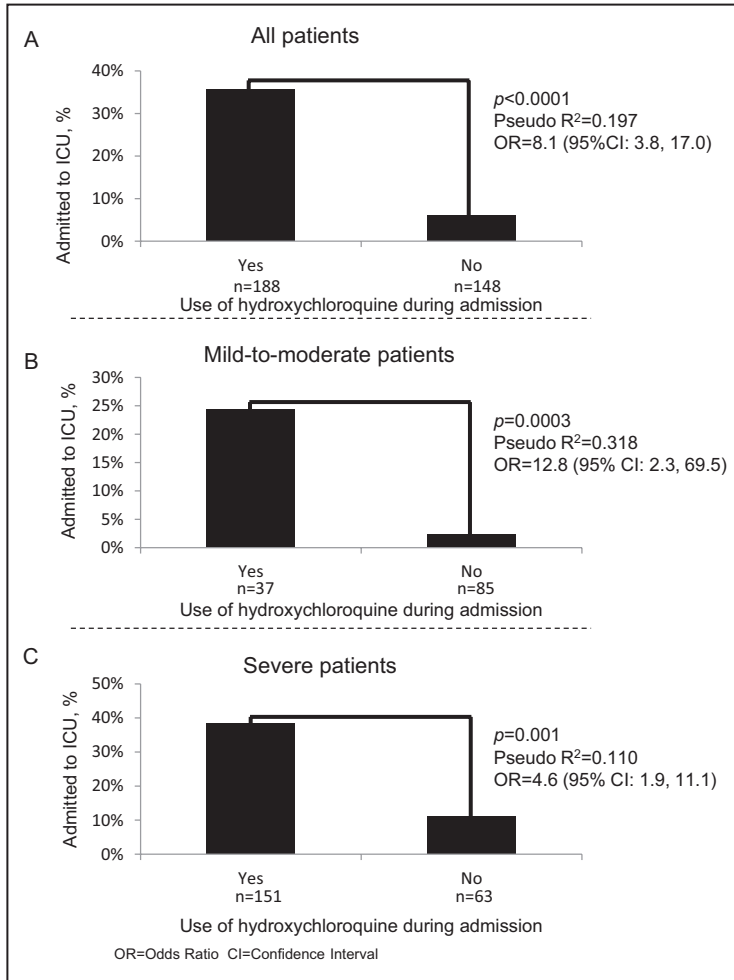
Table 2. Impact of Demographic Factors, Comorbidities, and Hydroxychloroquine Use on Risk of ICU Admission, Overall and by COVID-19 Symptom Severity

Variable	Odds Ratio for ICU Amission (95% CI)		
	All Patients	**Mild to Moderate Symptoms**	**Severe Symptoms**
HCQ use	8.05 (3.8-17.02)	12.75 (2.34-69.54)	4.6 (1.90-11.12)
Age (older)	1.00 (0.98-1.02)	1.00 (0.96-1.04)	1.00 (0.97-1.02)
Gender (male)	1.17 (0.66-2.10)	1.44 (0.32-6.52)	1.32 (0.69-2.56)
Obesity	1.26 (0.69-2.31)	4.81 (0.94-24.73)	1.03 (0.51-2.06)
Diabetes	1.09 (0.59-2.03)	2.18 (0.48-9.89)	0.94 (0.48-1.87)

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; HCQ, hydroxychloroquine; ICU, intensive care unit.

Figure 2. Association of hydroxychloroquine use with need for intubation, by disease severity.
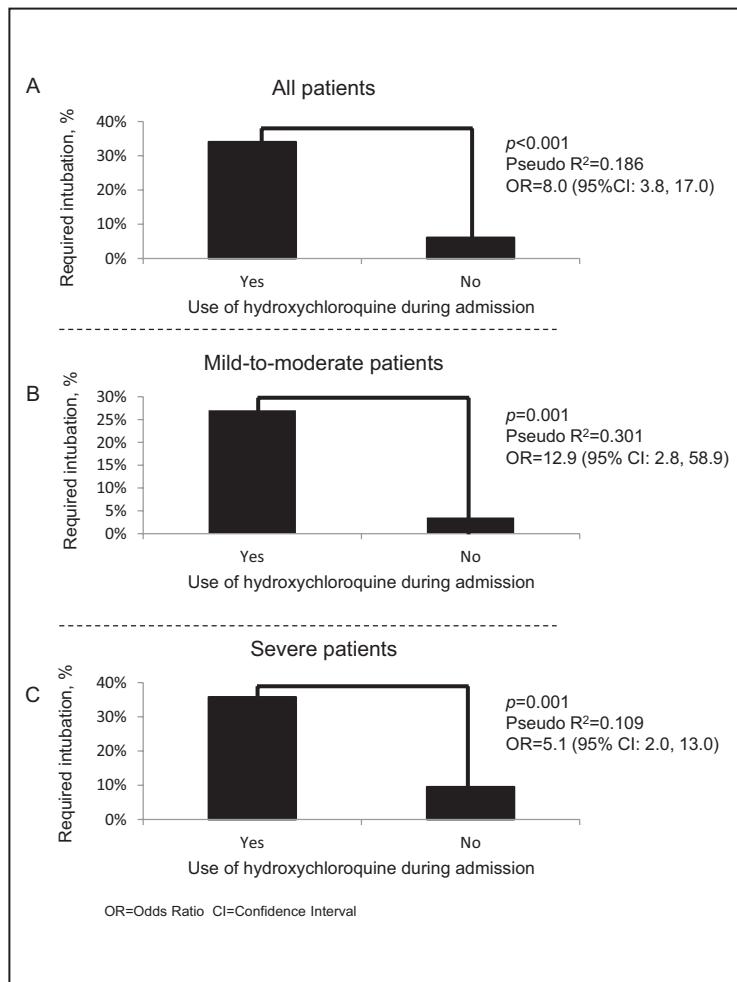
or moderate symptoms and patients with severe symptoms on admission or upon hydroxychloroquine initiation.

In our institution's protocol, hydroxychloroquine ordering was restricted to the infectious diseases physicians, which allowed for randomization of our patient population according to whether or not they were seen by infectious diseases physicians on admission. Depending on their decision to start treatment, we were able to separate patients into 2 separate cohorts: those who were and those who were not treated with hydroxychloroquine. Only 3% (11 of 336) of our patients received azithromycin in combination with hydroxychloroquine due to a lack of validated benefit in the literature and the additive cardiotoxic, QT interval–prolonging effects that can occur when using both agents. Most patients who were empirically receiving azithromycin at the time of hydroxychloroquine initiation were switched to an alternative antibiotic without QT-prolonging effects.

Our results suggest that patients presenting with mild, moderate, or severe symptoms who received hydroxychloroquine were at higher risk for both admission to the ICU and requiring intubation. These results were sustained after adjusting for disease severity on the basis of clinical symptoms. Although the mechanism of action of hydroxychloroquine is not fully understood, one possible explanation of our results may be hydroxychloroquine's immunomodulatory effects rather than its proposed antiviral effects. Hydroxychloroquine has been shown to inhibit various proinflammatory cytokines, such as tumor necrosis factor α, interleukin (IL)-1 and IL-6, and was suspected to mediate the effects of cytokine storm associated with COVID-19.[5] However, hydroxychloroquine may impact other protective mediators of the immune response in patients infected with SARS-CoV-2, which may have contributed to the observed clinical deterioration in patients treated with it in our study. Further research trials are needed to validate hydroxychloroquine's immunomodulatory effects, specifically in COVID-19.

Our study had several limitations. First, the mortality difference between groups may have been underestimated because some patients who were discharged home actually received hospice care at home due to their overall poor prognosis. Although we did not observe any statistical differences in mortality between the groups, approximately 12.8% of patients (43 of 336) were still admitted to the hospital at the time of data analysis. Second, we did not collect information regarding prognostic laboratory values such as C-reactive protein (CRP), lactate dehydrogenase (LDH), or D-dimer levels on admission, which may have suggested earlier signs of a hyperinflammatory immune response. However, elevations in CRP, LDH, and D-dimer have all been shown to correlate with more severe clinical symptoms, such as requirement of oxygen therapy, in patients with COVID-19.[19] Third, patients may have been coinfected with underlying bacterial infections on admission, which could have contributed to clinical outcomes. Previously reported data from China found that only 3.7% of patients with nonsevere COVID-19 (19 of 516) and 13.7% (16 of 117) of those with severe symptoms (16 of 117) had procalcitonin levels of >0.5 ng/mL, suggesting the relatively low incidence of a bacterial coinfection in COVID-19.[19] Procalcitonin levels were not measured on admission in our patient population

Table 3. Impact of Demographic Factors, Comorbidities, and Hydroxychloroquine Use on Risk of Intubation, Overall and by COVID-19 Symptom Severity

	Odds Ratio for Intubation (95% CI)		
Variable	All Patients	Mild to Moderate Symptoms	Severe Symptoms
HCQ use	7.99 (3.76-16.91)	12.91 (2.83-58.90)	5.08 (1.99-12.96)
Age (older)	1.01 (0.99-1.02)	1.02 (0.98-1.06)	1.00 (0.98-1.02)
Gender (male)	1.35 (0.75-2.42)	3.25 (0.79-12.28)	1.29 (0.66-2.53)
Obesity	1.19 (0.64-2.20)	4.41 (1.01-19.28)	0.95 (0.47-1.94)
Diabetes	0.95 (0.50-1.78)	1.59 (0.38-6.64)	0.87 (0.43-1.76)

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; HCQ, hydroxychloroquine.

Figure 3. Trends in cumulative survival and length of stay according to use vs nonuse of hydroxychloroquine.
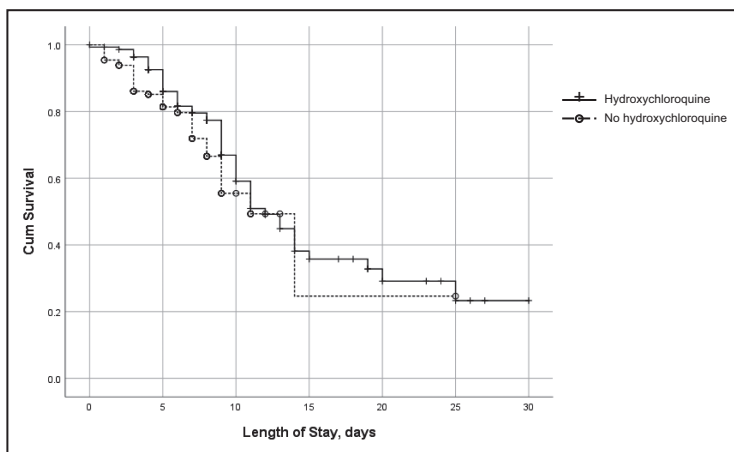
due to laboratory constraints; therefore, many patients received empiric antibiotic therapy on admission to cover for possible community-acquired pneumonia. Lastly, there may have been other confounding variables we did not account for in our data set, including use of other pharmacologic and nonpharmacologic investigational agents. Despite these limitations, our findings are consistent with the current IDSA guideline recommendation against hydroxychloroquine use for the treatment of COVID-19.[4]

Conclusion

In our retrospective cohort study involving hospitalized patients with COVID-19, hydroxychloroquine use was associated with disease progression, as indicated by increased rates of ICU admission and intubation. Hydroxychloroquine use was not associated with lower hospital LOS or lower mortality. Therefore, due to the drug's adverse effect profile, lack of clinical benefit, and potential for worsening the disease, we do not recommend hydroxychloroquine as a treatment option for COVID-19 outside of its current investigational use at this time. Further prospective, randomized controlled trials are needed to clarify the potential role of hydroxychloroquine in management of COVID-19.

Disclosures

The authors have declared no potential conflicts of interest.

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