International Journal of Infectious Diseases 97 (2020) 396–403

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19

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ARTICLE INFO

Article history:
Received 28 May 2020
Received in revised form 22 June 2020
Accepted 29 June 2020

Keywords:
Hydroxychloroquine
Mortality
COVID-19
SARS-COV-2
Coronavirus
Therapy

ABSTRACT

Significance: The United States is in an acceleration phase of the COVID-19 pandemic. Currently there is no known effective therapy or vaccine for treatment of SARS-CoV-2, highlighting urgency around identifying effective therapies.
Objective: The purpose of this study was to evaluate the role of hydroxychloroquine therapy alone and in combination with azithromycin in hospitalized patients positive for COVID-19.
Design: Multi-center retrospective observational study.
Setting: The Henry Ford Health System (HFHS) in Southeast Michigan: large six hospital integrated health system; the largest of hospitals is an 802-bed quaternary academic teaching hospital in urban Detroit, Michigan.
Participants: Consecutive patients hospitalized with a COVID-related admission in the health system from March 10, 2020 to May 2, 2020 were included. Only the first admission was included for patients with multiple admissions. All patients evaluated were 18 years of age and older and were treated as inpatients for at least 48 h unless expired within 24 h.
Exposure: Receipt of hydroxychloroquine alone, hydroxychloroquine in combination with azithromycin, azithromycin alone, or neither.
Main outcome: The primary outcome was in-hospital mortality.
Results: Of 2,541 patients, with a median total hospitalization time of 6 days (IQR: 4–10 days), median age was 64 years (IQR:53–76 years), 51% male, 56% African American, with median time to follow-up of 28.5 days (IQR:3–53). Overall in-hospital mortality was 18.1% (95% CI:16.6%–19.7%); by treatment: hydroxychloroquine + azithromycin, 157/783 (20.1% [95% CI: 17.3%–23.0%]), hydroxychloroquine alone, 162/1202 (13.5% [95% CI: 11.6%–15.5%]), azithromycin alone, 33/147 (22.4% [95% CI: 16.0%–30.1%]), and neither drug, 108/409 (26.4% [95% CI: 22.2%–31.0%]). Primary cause of mortality was respiratory failure (88%); no patient had documented torsades de pointes. From Cox regression modeling, predictors of mortality were age≥65 years (HR:2.6 [95% CI:1.9–3.3]), white race (HR:1.7 [95% CI:1.4–2.1]), CKD (HR:1.7 [95%CI:1.4–2.1]), reduced O2 saturation level on admission (HR:1.5 [95%CI:1.1–2.1]), and ventilator use during admission (HR: 2.2 [95%CI:1.4–3.3]). Hydroxychloroquine provided a 66% hazard ratio reduction, and hydroxychloroquine + azithromycin 71% compared to neither treatment ($p < 0.001$).
Conclusions and relevance: In this multi-hospital assessment, when controlling for COVID-19 risk factors, treatment with hydroxychloroquine alone and in combination with azithromycin was associated with reduction in COVID-19 associated mortality. Prospective trials are needed to examine this impact.

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https://doi.org/10.1016/j.ijid.2020.06.099
1201-9712/

Introduction

As of May 27, 2020, there were over 1,678,843 confirmed cases of COVID-19 claiming more than 100,000 lives in the Unites States (CDC, 2020). Currently there is no known effective therapy or vaccine. The urgent need for therapeutic agents has resulted in repurposing and redeployment of experimental agents (McCreary and Pogue, 2020; Sanders et al., 2020).

Hydroxychloroquine, an antimalarial and immunomodulatory agent and a safer analogue of chloroquine, has demonstrated antiviral activity against SARS-CoV-2 (Wang et al., 2020a; Liu et al., 2020; Yao et al., 2020; WHO, 2017). It is postulated to exert a direct antiviral activity by increasing intracellular pH resulting in decreased phago-lysosome fusion, impairing viral receptor glycosylation. In addition, it has immune-modulating effect by inhibiting toll-like receptor signaling, decreasing production of cytokines especially IL-1 and IL-6 (Savarino et al., 2003). Prior data also suggests a potential anti-thrombotic effect (Jung et al., 2010). Azithromycin, a macrolide antibiotic, has *in vitro* antiviral properties such as decreased viral replication, blocking entrance into host cells, and a potential immunomodulating effect (Tran et al., 2019). An *in vitro* study demonstrated synergistic activity of the combination of hydroxychloroquine and azithromycin against SARS-CoV-2 (Andreani et al., 2020). A small non-randomized, open-label trial from France reported higher frequency of SARS-CoV-2 clearance after six days of treatment with hydroxychloroquine alone or hydroxychloroquine in combination with azithromycin versus untreated control group (70% vs 12.5%; $P < 0.001$) (Gautret et al., 2020a). Other early studies of hydroxychloroquine have reported conflicting results (Gao et al., 2020; Gautret et al., 2020b; Chen et al., 2020a; Tang et al., 2020; Chen et al., 2020b; Yu et al., 2020; Geleris et al., 2020; Rosenberg et al., 2020; Magagnoli et al., 2020; Million et al., 2020). The US FDA as of June 15, 2020 has revoked the prior emergency use authorization (EUA) to use hydroxychloroquine and chloroquine to treat COVID-19 in certain hospitalized patients when clinical trial data is unavailable or participation is not feasible (FDA, 2020).

Currently, randomized trials of hydroxychloroquine for treatment and chemoprophylaxis are underway (NIH, 2020a; NIH, 2020b; NIH, 2020c; Pagliano et al., 2020). Based on these early reports, hydroxychloroquine alone and in combination with azithromycin was incorporated into our institutional clinical guidelines for the treatment of hospitalized patients with COVID-19. We examined the association between hydroxychloroquine use and mortality in a large cohort of hospitalized COVID-19 patients.

Methods

Setting

This is a comparative retrospective cohort study evaluating clinical outcomes of all consecutive patients hospitalized at the Henry Ford Health System (HFHS) in Southeast Michigan being treated for COVID-19. The organization is a large six hospital integrated health system; the largest of hospitals is an 802-bed quaternary academic teaching hospital in urban Detroit, Michigan. Approval for this study was granted by the Henry Ford Hospital IRB (#13897).

Patients

Patients with a COVID-related admission in the health system from March 10, 2020 to May 2, 2020 were included. Only the first admission was included for patients with multiple admissions. All patients were hospitalized though our emergency department. A COVID-related admission was defined as hospitalization during which the patient had a positive SARS-CoV-2 test. Diagnosis with SARS-CoV-2 was confirmed by a positive reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay from a nasopharyngeal sample. All patients evaluated were 18 years of age and older and were treated as inpatients for at least 48 h unless they died within the time period. The primary objective was to assess treatment experience with hydroxychloroquine versus hydroxychloroquine + azithromycin, azithromycin alone, and other treatments for COVID-19. Treatments were protocol driven, uniform in all hospitals and established by a system-wide interdisciplinary COVID-19 Task Force. Hydroxychloroquine was dosed as 400 mg twice daily for 2 doses on day 1, followed by 200 mg twice daily on days 2–5. Azithromycin was dosed as 500 mg once daily on day 1 followed by 250 mg once daily for the next 4 days. The combination of hydroxychloroquine + azithromycin was reserved for selected patients with severe COVID-19 and with minimal cardiac risk factors. An electrocardiogram (ECK) based algorithm was utilized for hydroxychloroquine use. QTc > 500 ms was considered an elevated cardiac risk and consequently hydroxychloroquine was reserved for patients with severe disease with telemetry monitoring and serial QTc checks. The clinical guidelines included adjunctive immunomodulatory therapy with corticosteroids and tocilizumab.

Data sources

The data source for analysis of patient information was derived from electronic medical records in the Electronic Information System. Study variables collected on each patient included the following; (1) patient demographics: age, gender, race, body mass index (BMI) on admission, stratified into four categories: <18.5; 18.5–24.9; 25.0–29.9 and ≥30; (2) clinical characteristics: admission date, discharge date, length of stay (LOS), comorbidities including: cardiovascular disease (CVD), chronic lung disease, chronic kidney disease (CKD), hypertension, asthma, chronic obstructive pulmonary disease (COPD), diabetes mellitus, immunodeficiency, and cancer (defined as active or past/resolved). Additionally, intensive care unit (ICU) status and ventilator use at any point during admission, minimum O2 saturation level collected on day of admission in the emergency department, and the maximal modified Sequential Organ Failure Assessment (mSOFA) score on admission were also collected. The mSOFA score is predictive of ICU mortality utilizing similar accuracy to the full SOFA score without substantial lab testing (ABG, LFTs) to complete (Grissom et al., 2010). The duration and dosages of all therapies for COVID-19 were collected.

Study endpoint

The primary endpoint was in-patient hospital mortality in each treatment group. All deaths were reviewed in detail by the study team.

Statistical analysis

Demographic and clinical characteristics were descriptively summarized for all patients and subsets by treatment group, to test the null hypothesis that treatment course between hydroxychloroquine, hydroxychloroquine + azithromycin, azithromycin, and other (no hydroxychloroquine or azithromycin) were similar. Multivariable Cox regression models and Kaplan–Meier survival curves were used to compare survival among treatment groups while controlling for demographics (e.g., age, gender), preexisting medical conditions (e.g. CVD, lung disease) and clinical disease severity (mSOFA, O2 saturation). Bivariate comparisons of the 4

medication groups were made using analysis of variance or Kruskal–Wallis tests for continuous variables, and chi-square tests or Fisher exact tests for categorical variables. Additional analysis was performed using propensity score matching to compare outcomes in mortality across treatment groups. A propensity score was created for each patient based on the set of patient characteristics used in the Cox regression model. Subsequently, 1 to 1 matchups of patients given hydroxychloroquine (either hydroxychloroquine alone or in combination with azithromycin) and patients not given hydroxychloroquine based on the exact propensity score were observed. The resulting matched group status was placed into its own Cox regression model as a mortality predictor with a Kaplan–Meier plot summarizing the survival curves of the two matched groups. P values <0.05 were considered statistically significant. Additionally, median survival times by treatment strata were calculated to approximate prognosis. No imputations were made for missing data. All data were analyzed using SPSS software version 26 (IBM SPSS Statistics for Windows, version 26, IBM Corp., Armonk, N.Y., USA) and STATA (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC), and SAS version 9.4.

Results

The first COVID-19 case confirmed at HFHS by RT-PCR was on March 10, 2020, any patients admitted before March 10th and subsequently tested positive were also included in the analyses. There was a total of 2,948 COVID-19 admissions, of these, 267 (9%) patients had not been discharged, 15 (0.5%) left against medical advice, and four (0.1%) were transferred to another healthcare facility; these patients were excluded from analysis as we could not ascertain their outcome. In addition, there were 121 (4.1%) readmissions, which were also excluded.

Overall, 2,541 consecutive patients were included in the analyses with a median age of 64 years (IQR: 53–76 years), 51% male, 56% African American, median inpatient LOS was 6 days (IQR: 4–10 days). The median time to follow-up was 28.5 days (IQR 3–53). The majority of patients (52%, n = 1,250) had BMI ≥ 30. Additional underlying comorbidities are detailed in Table 1. On the day of admission, two variables predicting severity of disease and mortality, highest mSOFA score and lowest O2 saturation, were recorded. However, 25% of the population did not have mSOFA scores available, as recording of this metric became institutional standard one month after the index admission. Other indicators of severity were ICU admission and mechanical ventilation status. All baseline characteristics were further stratified by the four treatment groups (hydroxychloroquine alone, hydroxychloroquine + azithromycin, azithromycin alone, and neither treatment). Median time (IQR) from admission to receipt of hydroxychloroquine was 1 day (1–2). Overall crude mortality rates were 18.1% in the entire cohort, 13.5% in the hydroxychloroquine alone group, 20.1% among those receiving hydroxychloroquine + azithromycin, 22.4% among the azithromycin alone group, and 26.4% for neither drug ($p < 0.001$). Adjunct therapy with corticosteroids (methylprednisolone and/or prednisone) and anti-IL-6 tocilizumab was provided in 68% and 4.5% of patients, respectively.

Primary cause of mortality in the 460 patients was: 88% respiratory failure, 4% cardiac arrest (with mean QTc interval from last ECG reading 471 ms), 8% other cardiopulmonary arrest and multi-organ failure. No patient had documented torsades de pointes.

In the multivariable Cox regression model of mortality using the group receiving neither hydroxychloroquine or azithromycin as the reference, treatment with hydroxychloroquine alone decreased the mortality hazard ratio by 66% ($p < 0.001$), and hydroxychloroquine + azithromycin decreased the mortality hazard ratio by 71% ($p < 0.001$). We did not find statistical significance in the relative effect of adjunct therapy and mortality. Predictors of mortality were age ≥65 years (HR, 2.6 [95% CI: 1.9, 3.3]), white race (HR: 1.7 [95% CI: 1.4, 2.1]), CKD (HR, 1.7 [95%CI: 1.4, 2.1]), reduced O2 saturation level on admission (HR, 1.6 [95%CI: 1.1, 2.2]), and ventilator use during admission (HR, 2.2 [95%CI: 1.4, 3.0]), which were all significantly associated with mortality due to COVID-19 (Table 2).

Kaplan–Meier survival curves showed significantly improved survival among patients in the hydroxychloroquine alone and hydroxychloroquine + azithromycin group compared with groups not receiving hydroxychloroquine and those receiving azithromycin alone (Figure 1). The survival curves suggest that the enhanced survival in the hydroxychloroquine alone group persists all the way out to 28 days from admission.

Further, a total of 190 hydroxychloroquine patients exactly matched up with 190 corresponding non-hydroxychloroquine treated patients based on the exact underlying propensity score. Table 3 contains a descriptive summarization of these patients within both the unmatched and propensity matched settings, confirming that the propensity matched groups have identical underlying patient characteristics. The Cox regression result for the two propensity matched groups (Table 4) indicates that treatment with hydroxychloroquine resulted in a mortality hazard ratio decrease of 51% ($p = 0.009$). The resulting Kaplan–Meier survival curves within the propensity matched setting displayed significantly better survival in the hydroxychloroquine treated group, with the enhanced survival persisting all the way out to 28 days from admission (Figure 2).

Discussion

The results of this study demonstrate that in a strictly monitored protocol-driven in-hospital setting, treatment with hydroxychloroquine alone and hydroxychloroquine + azithromycin was associated with a significant reduction in mortality among patients hospitalized with COVID-19. In this study, among one of the largest COVID-19 hospital patient cohorts (n = 2,541) assembled in a single institution, overall in-hospital COVID-19 associated mortality was 18.1% reflecting a high prevalence of co-morbid conditions in COVID-19 patients admitted to our institution. The independent predictors of mortality in our study included age ≥65 years, CKD, and severe illness at initial presentation as measured by the oxygen saturation levels on admission, and ventilator use reflect findings similar to those reported in earlier studies (Rio and Malani, 2020). These predictors also underscore the high-risk for COVID-19 experienced by residents in our hospital catchment population in Metropolitan Detroit, Michigan. Michigan is among the states with the highest number of cases of COVID-19 and deaths. In Detroit, our residents suffer from substantial preexisting social and racial health disparities that place our patients at increased risk of severe disease and higher mortality (CDC, 2020).

In the present study, multivariate analysis performed using Cox regression modeling and propensity score matching to control for potential confounders affirmed that treatment with hydroxychloroquine alone and hydroxychloroquine in combination with azithromycin was associated with higher survival among patients with COVID-19. Patients that received neither medication or azithromycin alone had the highest cumulative hazard. The benefits of hydroxychloroquine in our cohort as compared to previous studies maybe related to its use early in the disease course with standardized, and safe dosing, inclusion criteria, comorbidities, or larger cohort. The postulated pathophysiology of COVID-19 of the initial viral infection phase followed by the hyperimmune response suggest potential benefit of early administration of hydroxychloroquine for its antiviral and antithrombotic

Table 1
Patient characteristics by treatment group.

Characteristics		Total (n = 2541)	Neither Med (n = 409)	HCQ alone (n = 1202)	AZM alone (n = 147)	HCQ + AZM (n = 783)	P-value
Mortality, n (%)		460 (18.1)	108 (26.4)	162 (13.5)	33 (22.4)	157 (20.1)	<0.001***
Hospital LOS in days,		8.3 ± 6.5,	5.6 ± 4.8,	8.0 ± 5.8,	5.3 ± 4.5,	10.7 ± 7.5,	<0.001***
Mean ± SD, median (IQR)		6 (4–10)	(4 (3–7)	6 (4–10)	4 (2–6)	8 (5–14)	
Age in years,		63.7 ± 16.5,	68.1 ± 18.9,	63.2 ± 15.6,	63.3 ± 17.3,	62.3 ± 15.9,	<0.001***
Mean ± SD, median (IQR)		64 (53–76)	71 (56–83)	64 (53–74)	64 (52–76)	62 (51–74)	
Age,	<65 years	1278 (50.3)	158 (38.6)	614 (51.1)	79 (53.7)	427 (54.5%)	<0.001***
n (%)	≥65 years	1263 (49.7)	251 (61.4)	588 (48.9)	68 (46.3)	356 (45.5%)	
Gender,	Male	1298 (51.1)	199 (48.7)	634 (52.8)	62 (42.2)	403 (51.5%)	0.072
n (%)	Female	1243 (48.9)	210 (51.3)	568 (47.2)	85 (57.8)	380 (48.5%)	
Race,	Black	1411 (55.5)	187 (45.7)	724 (60.2)	76 (51.7)	424 (54.2%)	<0.001***
n (%)	White	852 (33.5)	186 (45.5)	332 (27.6)	63 (42.9)	271 (34.6%)	
	Asian/Pacific Islander	47 (1.8)	6 (1.5)	24 (2.0)	0 (0.0)	17 (2.2%)	
	Other	231 (9.1)	30 (7.3)	122 (10.1)	8 (5.4)	71 (9.1%)	
BMI,		31.7 ± 8.5,	28.8 ± 7.6,	31.9 ± 8.6,	31.4 ± 8.7,	32.9 ± 8.4,	<0.001***
Mean ± SD, median (IQR)		30 (26–36)	28 (23–33)	30 (26–36)	29 (25–36)	32 (27–37)	
BMI,	<18.5	48 (2.0)	22 (5.7)	15 (1.4)	3 (2.1)	8 (1.1%)	<0.001***
n (%)	18.5–24.9	430 (18.0)	108 (28.2)	198 (17.9)	25 (17.5)	99 (13.1%)	
	25.0–29.9	662 (27.7)	104 (27.2)	314 (28.4)	49 (34.3)	195 (25.8%)	
	≥30.0	1250 (52.3)	149 (38.9)	580 (52.4	66 (46.2)	455 (60.1%)	
Chronic lung disease, n (%)		1619 (63.7)	195 (47.7)	806 (67.1)	93 (63.3)	525 (67.0)	<0.001***
Immunodeficiency, n (%)		30 (1.2)	2 (0.5)	15 (1.2)	2 (1.4)	11 (1.4)	0.502
Cardiovascular disease, n (%)		222 (8.7)	45 (11.0)	100 (8.3)	10 (6.8)	67 (8.6)	0.306
Chronic kidney disease, n (%)		1099 (43.3)	196 (47.9)	528 (43.9)	62 (42.2)	313 (40.0)	0.062
COPD, n (%)		325 (12.8)	58 (14.2)	144 (12.0)	24 (16.3)	99 (12.6)	0.380
Hypertension, n (%)		1663 (65.4)	256 (62.6)	807 (67.1)	93 (63.3)	507 (64.8)	0.324
Asthma, n (%)		251 (9.9)	28 (6.8)	130 (10.8)	19 (12.9)	74 (9.5)	0.069
Cancer, n (%)		380 (15.0)	78 (19.1)	165 (13.7)	17 (11.6)	120 (15.3)	0.041*
Diabetes mellitus, n (%)		955 (37.6)	130 (31.8)	484 (40.3)	45 (30.6)	296 (37.8)	0.006**
Max mSOFA score on admission,		3.7 ± 3.0,	4.0 ± 3.6,	3.2 ± 2.7,	5.0 ± 3.9,	4.2 ± 3.1,	<0.001***
Mean ± SD, median (IQR)		3 (1–5)	3 (1–6)	3 (1–5)	4 (2–6)	4 (2–6)	
mSOFA	≤1	497 (26.4)	92 (31.5)	295 (28.5)	12 (19.7)	98 (20.0%)	<0.001***
score,	2–4	799 (42.5)	95 (32.5)	481 (46.4)	19 (31.1)	204 (41.5%)	
n (%)	≥5	584 (31.1)	105 (36.0)	260 (25.1)	30 (49.2)	189 (38.5%)	
Max O2 saturation on admission,		90.0 ± 8.1,	89.8 ± 10.9,	90.5 ± 6.7,	90.7 ± 8.7,	89.2 ± 8.1,	<0.001***
Mean ± SD, median (IQR)		(92 (89–94)	93 (89–95)	92 (89–94)	92 (90–94)	91 (88–93)	
O2 saturation,	Normal (≥95%)	504 (19.8)	126 (30.8)	233 (19.4)	34 (23.1)	111 (14.2%)	<0.001***
n (%)	mild hypoxemia (90–94%)	1275 (50.2)	180 (44.0)	619 (51.5)	84 (57.1)	392 (50.1%)	
	Mod hypoxemia (86–89%)	408 (16.1)	38 (9.3)	202 (16.8)	13 (8.8)	155 (19.8%)	
	Severe hypoxemia (≤85%)	354 (13.9)	65 (15.9)	148 (12.3)	16 (10.9)	125 (16.0%)	
Ever in ICU, n (%)		614 (24.2%)	62 (15.2)	243 (20.2)	19 (12.9)	290 (37.0)	<0.001***
Total ICU days,		2.3 ± 5.3,	0.8 ± 2.9,	1.9 ± 4.7,	0.7 ± 2.3,	4.9 ± 6.9,	<0.001***
Mean ± SD, median (IQR)		0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	(0–0)	
Ever mechanically ventilated, n (%)		448 (17.6%)	34 (8.3)	166 (13.8)	14 (9.5)	234 (29.9)	<0.001***
Total vent days,		1.6 ± 4.5,	0.5 ± 2.2,	1.2 ± 3.7,	0.5 ± 2.0,	3.1 ± 6.1,	<0.001***
Mean ± SD, median (IQR)		0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	
Given steroid, n (%)		1733 (68.2)	146 (35.7)	948 (78.9)	57 (38.8)	582 (74.3)	<0.001***
Given tocilizumab, n (%)		114 (4.5)	5 (1.2)	32 (2.7)	5 (3.4)	72 (9.2)	<0.001***

* alues between 0.01 and 0.05.
** P-values between 0.001 and 0.01.
*** P-values less than 0.001.

properties. Later therapy in patients that have already experienced hyperimmune response or critical illness is less likely to be of benefit. Others have shown that COVID-19 hospitalized patients are not diagnosed in the community and often rapidly deteriorate when hospitalized with fulminant illness (Mc McCullough and Arunthamakun, 2020).

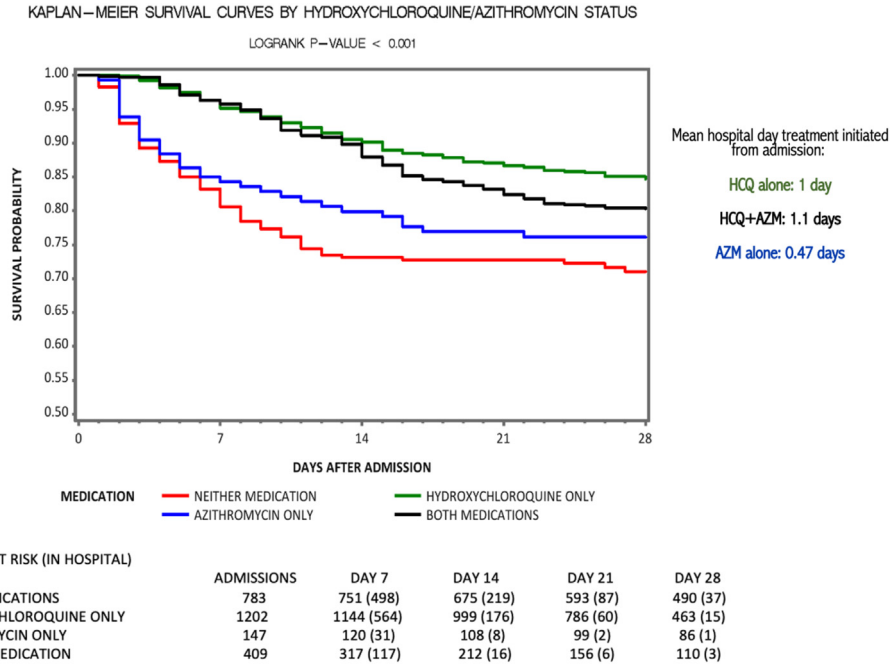
Limitations to our analysis include the retrospective, non-randomized, non-blinded study design. Also, information on duration of symptoms prior to hospitalization was not available for analysis. However, our study is notable for use of a cohort of consecutive patients from a multi-hospital institution, regularly updated and standardized institutional clinical treatment guidelines and a QTc interval-based algorithm specifically designed to ensure the safe use of hydroxychloroquine. To mitigate potential limitations associated with missing or inaccurate documentation in electronic medical records, we manually reviewed all deaths to confirm the primary mortality outcome and ascertain the cause of death. A review of our COVID-19 mortality data demonstrated no major cardiac arrhythmias; specifically, no torsades de pointes that has been observed with hydroxychloroquine treatment. This finding may be explained in two ways. First, our patient population received aggressive early medical intervention, and were less prone to development of myocarditis, and cardiac inflammation commonly seen in later stages of COVID-19 disease. Second, and importantly, inpatient telemetry with established electrolyte protocols were stringently applied to our population and monitoring for cardiac dysrhythmias was effective in controlling for adverse events. Additional strengths were the inclusion of a multi-racial patient composition, confirmation of all patients for infection with PCR, and control for various confounding factors including patient characteristics such as severity of illness by propensity matching.

Recent observational retrospective studies and randomized trials of hydroxychloroquine have reported variable results (Gautret et al., 2020a; Gao et al., 2020; Gautret et al., 2020b; Chen et al., 2020a; Tang et al., 2020; Chen et al., 2020b; Yu et al., 2020; Geleris et al., 2020; Rosenberg et al., 2020; Magagnoli et al., 2020; Million et al., 2020). In a randomized controlled study of 62 patients from China with COVID-19, hydroxychloroquine was

Table 2
Multivariable cox regression model for mortality prediction.

Parameter	P-value	Hazard ratio	95% Hazard ratio confidence limits	
HCQ alone (vs. neither medication)	<0.001***	0.340	0.254	0.455
Azithromycin alone (vs. neither medication)	0.825	1.050	0.682	1.616
HCQ + AZM (vs. neither medication)	<0.001***	0.294	0.218	0.396
Age ≥ 65 years	<0.001***	2.579	1.989	3.345
M gender	0.155	1.157	0.946	1.414
White race	<0.001***	1.738	1.413	2.137
BMI ≥ 30	0.021*	0.775	0.624	0.962
Lung comorbidity	0.393	0.908	0.727	1.134
Immunodeficiency comorbidity	0.429	1.398	0.609	3.206
Cardiovascular comorbidity	0.678	1.062	0.800	1.410
Chronic kidney disease comorbidity	<0.001***	1.699	1.370	2.108
COPD comorbidity	0.170	1.202	0.924	1.563
Hypertension comorbidity	0.064	0.798	0.628	1.014
Asthma comorbidity	0.643	0.916	0.632	1.327
Cancer comorbidity	0.577	0.933	0.731	1.190
Diabetes comorbidity	0.822	0.975	0.786	1.211
Percent O2 saturation < 95	0.021*	1.488	1.063	2.084
Admitted to ICU	0.882	0.969	0.635	1.478
Ventilator	<0.001***	2.159	1.427	3.268
Given steroid	0.085	0.802	0.625	1.031
Given tocilizumab	0.490	0.894	0.651	1.228

* P-values between 0.01 and 0.05.
*** P-values less than 0.001.



NUMBER AT RISK (IN HOSPITAL)

	ADMISSIONS	DAY 7	DAY 14	DAY 21	DAY 28
BOTH MEDICATIONS	783	751 (498)	675 (219)	593 (87)	490 (37)
HYDROXYCHLOROQUINE ONLY	1202	1144 (564)	999 (176)	786 (60)	463 (15)
AZITHROMYCIN ONLY	147	120 (31)	108 (8)	99 (2)	86 (1)
NEITHER MEDICATION	409	317 (117)	212 (16)	156 (6)	110 (3)

Figure 1. Kaplan-Meier survival curves among treatment groups.

associated with a shortened duration of fever and time to cough and pneumonia resolution (Chen et al., 2020b). In contrast, a study of 1376 consecutive hospitalized COVID-19 patients in New York that used respiratory failure as the primary endpoint found no significant reduction in the likelihood of death or intubation among those receiving hydroxychloroquine compared to those who did not (Geleris et al., 2020). In a separate multicenter cohort study of 1438 patients from 25 hospitals in New York, no reduction in hospitalized patient mortality was observed with hydroxychloroquine treatment (Rosenberg et al., 2020). Among a number of limitations, this study included patients who were initiated on hydroxychloroquine therapy at any time during their hospitalization. In contrast, in our patient population, 82% received hydroxychloroquine within the first 24 h of admission, and 91% within 48 h of admission. Because treatment regimens likely varied substantially (including delayed initiation) across the 25 hospitals that contributed patients to the study, it is not surprising that the case-fatality rate among the New York patients was significantly higher than in our study.

Globally, the overall crude mortality from SARS-COV-2 is estimated to be approximately 6–7% (CDC, 2020; WHO, 2020). Multiple descriptive studies report higher mortality in hospitalized COVID-19 patients from 10–30% (Huang et al., 2020; Zhou et al., 2020; Wu et al., 2020; Wang et al., 2020b; Guan et al., 2020; Richardson et al., 2020; Arentz et al., 2020; Cao et al., 2020; Grein et al., 2020). Not surprisingly, mortality as high as 58% was observed among patients requiring ICU care and mechanical ventilation (Guan et al., 2020; Richardson et al., 2020). This high

Table 3
Characteristics of patients given versus not given HCQ before and after propensity score matching.

Characteristics	Unmatched patients		Propensity-MATCHED patients	
	Given HCQ (N = 1985)	Not given HCQ (N = 556)	Given HCQ (N = 190)	Not given HCQ (N = 190)
Age ≥ 65 years	944 (47.6%)	319 (57.4%)	96 (50.5%)	96 (50.5%)
Male gender	1037 (52.2%)	261 (46.9%)	88 (46.3%)	88 (46.3%)
White race	603 (30.4%)	249 (44.8%)	67 (35.3%)	67 (35.3%)
BMI ≥ 30	1035 (55.5%)	215 (40.9%)	87 (45.8%)	87 (45.8%)
Lung comorbidity	1331 (67.1%)	288 (51.8%)	103 (54.2%)	103 (54.2%)
Immunodeficiency comorbidity	26 (1.3%)	4 (0.7%)	1 (0.5%)	1 (0.5%)
Cardiovascular comorbidity	167 (8.4%)	55 (9.9%)	7 (3.7%)	7 (3.7%)
Chronic kidney disease comorbidity	841 (42.4%)	258 (46.4%)	69 (36.3%)	69 (36.3%)
COPD comorbidity	243 (12.2%)	82 (14.7%)	10 (5.3%)	10 (5.3%)
Hypertension comorbidity	1314 (66.2%)	349 (62.8%)	118 (62.1%)	118 (62.1%)
Asthma comorbidity	204 (10.3%)	47 (8.5%)	6 (3.2%)	6 (3.2%)
Cancer comorbidity	285 (14.4%)	95 (17.1%)	8 (4.2%)	8 (4.2%)
Diabetes comorbidity	780 (39.3%)	175 (31.5%)	51 (26.8%)	51 (26.8%)
Percent O2 saturation ≤ 95	1641 (82.7%)	396 (71.2%)	141 (74.2%)	141 (74.2%)
Admitted to ICU	533 (26.9%)	81 (14.6%)	12 (6.3%)	12 (6.3%)
Ventilator	400 (20.2%)	48 (8.6%)	10 (5.3%)	10 (5.3%)
Given steroid	1530 (77.1%)	203 (36.5%)	84 (44.2%)	84 (44.2%)
Given tocilizumab	104 (5.2%)	10 (1.8%)	2 (1.1%)	2 (1.1%)

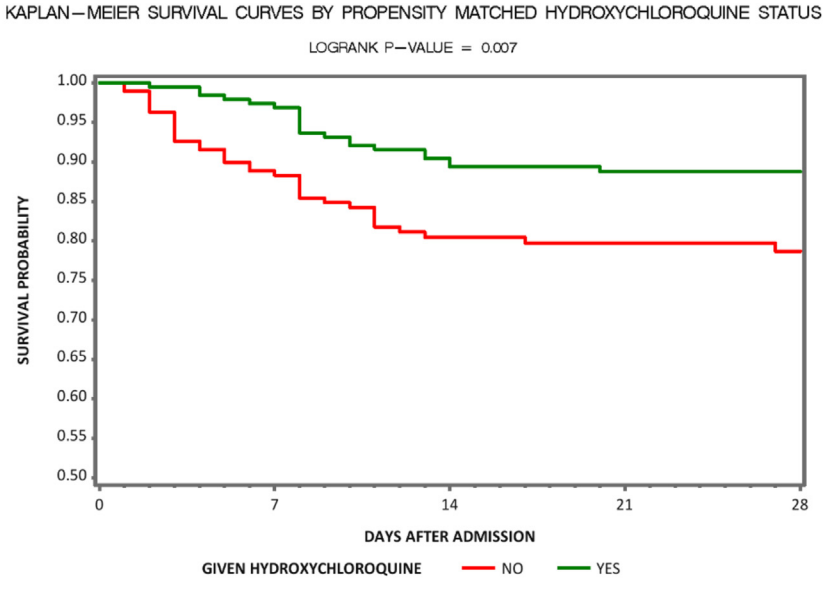
Table 4
Propensity matched cox regression result for mortality prediction.

Parameter	P-value	Hazard ratio	95% Hazard ratio confidence limits	
Given HCQ	0.009*	0.487	0.285	0.832

* P-value between 0.001 and 0.01.

mortality associated with COVID-19 in many populations has led to a search for effective drug therapies. The randomized controlled trial of lopinavir–ritonavir in COVID-19 hospitalized patients showed a mortality of 19.2% on lopinavir–ritonavir and 25% for standard of care; therapy had to be terminated in 13.8% patients due to adverse events (Arentz et al., 2020). In the compassionate use remdesivir trial, 13% mortality was observed in the cohort of 61 patients (Cao et al., 2020). The interim analysis randomized trial of remdesivir showed a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group (p = 0.059) (Grein et al., 2020). In our study, overall mortality was 18.1% and in ICU patients 45%. Our cohort included patients with severe disease, with 24% and 18% requiring ICU care and mechanical ventilation at presentation, respectively.

Findings of this observational study provide crucial data on experience with hydroxychloroquine therapy, providing necessary interim guidance for COVID-19 therapeutic practice. These findings do support the recent NIH guidelines (NIH, 2020a), indicating a potential role for hydroxychloroquine in treatment of hospitalized COVID-19 patients without co-administration of azithromycin. However, our results should be interpreted with some caution and should not be applied to patients treated outside of hospital settings. Our results also require further confirmation in



NUMBER AT RISK (IN HOSPITAL)

	ADMISSIONS	DAY 7	DAY 14	DAY 21	DAY 28
GIVEN HYDROXYCHLOROQUINE	190	184 (84)	164 (16)	146 (8)	111 (2)
NOT GIVEN HYDROXYCHLOROQUINE	190	158 (49)	118 (7)	98 (2)	72 (1)

Figure 2. Kaplan-Meier survival curves within the propensity matched setting.

prospective, randomized controlled trials that rigorously evaluate the safety and efficacy of hydroxychloroquine therapy for COVID-19 in hospitalized patients. Considered in the context of current studies on the use of hydroxychloroquine for COVID-19, our results suggest that hydroxychloroquine may have an important role to play in reducing COVID-19 mortality.

Funding

None, Internal Support Henry Ford Health System.

Conflict of interest

S.H. received speakers' bureau honoraria from Bayer. I.B. received speakers' bureau honoraria from Gilead, ViiV, and Jansssen, M.Z received consultation honoraria from contrafact. All others have no conflicts of interests.

Ethical approval

Approval for this study was granted by the Henry Ford Hospital Institutional Review Board (#13897).

Acknowledgements

David Allard, MD; Robert C Brooks; Erika Hadley; Gil Armon for assistance with data from the electronic medical record.

Appendix A

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