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Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State

Eli S. Rosenberg, PhD; Elizabeth M. Dufort, MD; Tomoko Udo, PhD; Larissa A. Wilberschied, MS; Jessica Kumar, DO; James Tesoriero, PhD; Patti Weinberg, PA; James Kirkwood, MPH; Alison Muse, MPH; Jack DeHovitz, MD; Debra S. Blog, MD; Brad Hutton, MPH; David R. Holtgrave, PhD; Howard A. Zucker, MD

IMPORTANCE Hydroxychloroquine, with or without azithromycin, has been considered as a possible therapeutic agent for patients with coronavirus disease 2019 (COVID-19). However, there are limited data on efficacy and associated adverse events.

OBJECTIVE To describe the association between use of hydroxychloroquine, with or without azithromycin, and clinical outcomes among hospital inpatients diagnosed with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS Retrospective multicenter cohort study of patients from a random sample of all admitted patients with laboratory-confirmed COVID-19 in 25 hospitals, representing 88.2% of patients with COVID-19 in the New York metropolitan region. Eligible patients were admitted for at least 24 hours between March 15 and 28, 2020. Medications, preexisting conditions, clinical measures on admission, outcomes, and adverse events were abstracted from medical records. The date of final follow-up was April 24, 2020.

EXPOSURES Receipt of both hydroxychloroquine and azithromycin, hydroxychloroquine alone, azithromycin alone, or neither.

MAIN OUTCOMES AND MEASURES Primary outcome was in-hospital mortality. Secondary outcomes were cardiac arrest and abnormal electrocardiogram findings (arrhythmia or QT prolongation).

RESULTS Among 1438 hospitalized patients with a diagnosis of COVID-19 (858 [59.7%] male, median age, 63 years), those receiving hydroxychloroquine, azithromycin, or both were more likely than those not receiving either drug to have diabetes, respiratory rate >22/min, abnormal chest imaging findings, O_2 saturation lower than 90%, and aspartate aminotransferase greater than 40 U/L. Overall in-hospital mortality was 20.3% (95% CI, 18.2%-22.4%). The probability of death for patients receiving hydroxychloroquine + azithromycin was 189/735 (25.7% [95% CI, 22.3%-28.9%]), hydroxychloroquine alone, 54/271 (19.9% [95% CI, 15.2%-24.7%]), azithromycin alone, 21/211 (10.0% [95% CI, 5.9%-14.0%]), and neither drug, 28/221 (12.7% [95% CI, 8.3%-17.1%]). In adjusted Cox proportional hazards models, compared with patients receiving neither drug, there were no significant differences in mortality for patients receiving hydroxychloroquine + azithromycin (HR, 1.35 [95% CI, 0.76-2.40]), hydroxychloroquine alone (HR, 1.08 [95% CI, 0.63-1.85]), or azithromycin alone (HR, 0.56 [95% CI, 0.26-1.21]). In logistic models, compared with patients receiving neither drug cardiac arrest was significantly more likely in patients receiving hydroxychloroquine + azithromycin (adjusted OR, 2.13 [95% CI, 1.12-4.05]), but not hydroxychloroquine alone (adjusted OR, 1.91 [95% CI, 0.96-3.81]) or azithromycin alone (adjusted OR, 0.64 [95% CI, 0.27-1.56]), . In adjusted logistic regression models, there were no significant differences in the relative likelihood of abnormal electrocardiogram findings.

CONCLUSIONS AND RELEVANCE Among patients hospitalized in metropolitan New York with COVID-19, treatment with hydroxychloroquine, azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality. However, the interpretation of these findings may be limited by the observational design.

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Supplemental content

Author Affiliations: University at Albany School of Public Health, State University of New York, Rensselaer (Rosenberg, Udo, Holtgrave); New York State Department of Health, Albany (Dufort, Wilberschied, Kumar, Tesoriero, Kirkwood, Muse, Blog, Hutton, Zucker); IPRO, Lake Success, New York (Weinberg, DeHovitz); Downstate Health Sciences University, State University of New York, Brooklyn (DeHovitz).

Corresponding Author: Eli S. Rosenberg, PhD, Department of Epidemiology and Biostatistics, University at Albany School of Public Health, One University Pl, Room 123, Albany, NY 12203 (erosenberg2@albany.edu).

The novel coronavirus disease 2019 (COVID-19) has resulted in the deaths of more than 248 000 persons worldwide as of May 4, 2020.[1,2] In the US, New York State has the largest disease and mortality burden.[3] As of May 4, 2020, more than 318 000 positive cases have been identified in New York and more than 19 400 individuals have died.[4]

Research is under way to identify vaccines and therapeutics for COVID-19, including repurposing of medications. Based on evidence from in vitro studies on the suppression of activity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other coronavirus strains, interest increased in the use of hydroxychloroquine and chloroquine with the possible addition of azithromycin for the treatment of COVID-19.[5-9] However, research has been limited by outcomes assessed, short follow-up, exclusion of patients still admitted, small sample size, and types of patients studied. Few studies have evaluated adverse events potentially linked to the use of hydroxychloroquine or chloroquine and azithromycin in patients with COVID-19, including electrophysiological cardiac conditions of prolonged QT and arrhythmia.[10-13] Based on available evidence, the US Food and Drug Administration authorized the emergency use of strategic national stockpile hydroxychloroquine and chloroquine in hospitalized patients when clinical trials were unavailable or not possible.[14]

Although randomized double-blind clinical trials are the optimal study design, given the urgent need to respond to the COVID-19 pandemic in New York an observational study was implemented to evaluate the clinical outcomes and adverse effects associated with hydroxychloroquine and azithromycin therapies for COVID-19. This multicenter retrospective cohort study used data from the State Health Information Network for NY (SHIN-NY), the state's public health information exchange network connecting New York State hospitals, supplemented by medical record reviews by trained chart abstractors. The aim was to understand prescribing patterns of hydroxychloroquine and azithromycin in hospitalized patients with COVID-19 and the association of these drugs with mortality and possible adverse events.

Key Points

Question Among patients with coronavirus disease 2019 (COVID-19), is there an association between use of hydroxychloroquine, with or without azithromycin, and in-hospital mortality?

Findings In a retrospective cohort study of 1438 patients hospitalized in metropolitan New York, compared with treatment with neither drug, the adjusted hazard ratio for in-hospital mortality for treatment with hydroxychloroquine alone was 1.08, for azithromycin alone was 0.56, and for combined hydroxychloroquine and azithromycin was 1.35. None of these hazard ratios were statistically significant.

Meaning Among patients hospitalized with COVID-19, treatment with hydroxychloroquine, azithromycin, or both was not associated with significantly lower in-hospital mortality.

Methods

Study Sample

This study received exempt status from the New York State Department of Health institutional review board as a secondary analysis of identifiable data originally collected for nonresearch purposes.

We analyzed a random sample of inpatients with laboratory-confirmed COVID-19 admitted to hospitals in the New York City (NYC) metropolitan region between March 15 and 28, 2020, during which time a rapid rise in COVID-19 hospitalizations was occurring. The region had 88.3% of COVID-19 cases in New York State at that time.[4] This 2-week sampling period was selected to ensure a sufficient number of patients whose discharge status was determined (alive or deceased), to afford sufficient follow-up time for patients still admitted, and to allow for a relatively balanced sample size between treatment (hydroxychloroquine with or without azithromycin) and comparison (no hydroxychloroquine) groups.

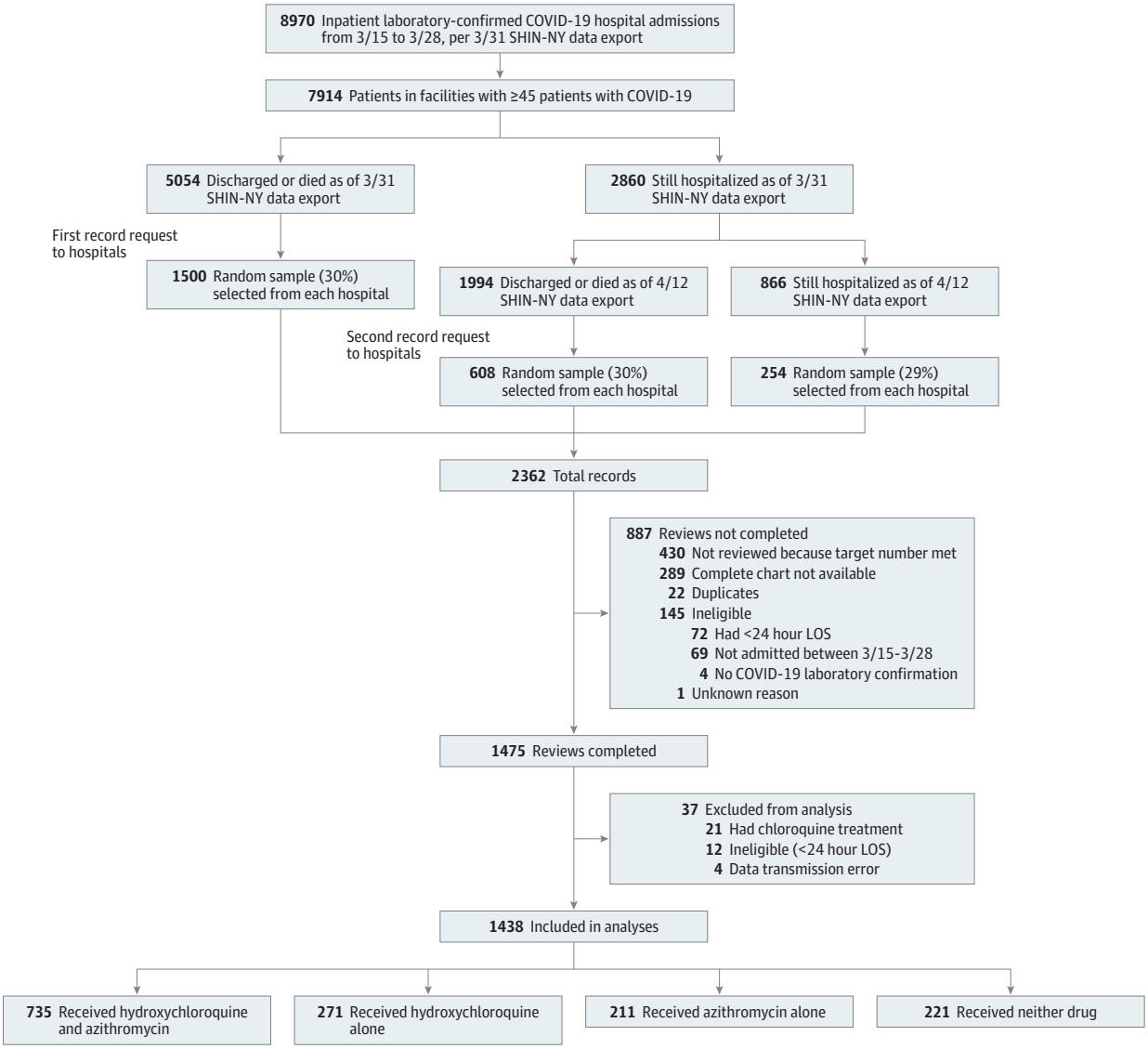
The New York State Department of Health electronic laboratory file of all reported COVID-19 cases was matched with the SHIN-NY data to create a list of all patients with laboratory-confirmed COVID-19 admitted during the sampling period to hospitals in NYC, Nassau County, Suffolk County, and all but one hospital in Westchester County. From this data set we established a sampling frame of all patients at 25 hospitals (88.2% of patients in the region) with a high volume of patients with COVID-19, defined as at least 45 discharges during the sampling period.

Patients were selected by hospital-stratified random sampling and their records were requested from each hospital, with additional records requested to allow removal due to ineligible and delayed records. Because full records are not available from hospitals until patient discharge or death, the cohort was assembled through 2 record requests on April 1 and 16 as patients were discharged or died. Data for the remaining 11% of those patients still admitted on April 12 were abstracted through patient portals of the 2 SHIN-NY qualified entities (**Figure 1**).

Records were abstracted between April 9 and 27 by a trained team of 12 nurses and 6 epidemiologists, under physician supervision, into a standardized digital form, based on a modified Centers for Disease Prevention and Control (CDC) COVID-19 abstraction form, and underwent daily quality-control checks (Supplement 1).[15] Following exclusion for reasons including discharge within 24 hours and chart too incomplete for review (Figure 1), a final sample of 1438 was obtained.

Information was collected on COVID-19 diagnosis, patient demographics, preexisting medical conditions, initial vital signs and laboratory test results within 24 hours of admission, and chest imaging findings to describe the cohort and as potential confounders. To examine whether racial or ethnic minority patients were less likely to receive hydroxychloroquine and/or azithromycin, race and ethnicity were measured in the following manner. Where available in a patient's medical chart, race was categorized as white, black, Asian/Pacific Islander, American Indian/Alaska Native, multiracial,

Figure 1. Sampling Strategy of COVID-19 Admissions in New York From Underlying Patient Cohort



COVID-19 indicates coronavirus disease 2019; LOS, length of stay; SHIN-NY, State Health Information Network for NY.

not specified, or not documented (ie, missing). Ethnicity was coded separately as either Hispanic/Latino, non-Hispanic/Latino, or unknown. Of 540 patients whose race/ethnicity information was missing in the charts, 462 were supplemented by race/ethnicity information available in the SHIN-NY data. The patients were then classified into the following mutually exclusive race and ethnicity categories for the final analyses: non-Hispanic white, non-Hispanic black, Hispanic, or other (Asian/Pacific Islander, American Indian/Alaska Native, multiracial, and not specified). Race or ethnicity of 78 (5.4%) patients whose information was unknown in their charts or the SHIN-NY data remained missing.

Exposure

Patients were categorized into 4 treatment groups based on having received at any time during hospitalization: (1) hydroxychloroquine with azithromycin, (2) hydroxychloroquine without azithromycin (hydroxychloroquine alone), (3) azithromycin alone, and (4) neither drug, defined as no receipt of either hydroxychloroquine or azithromycin in the record; other medications may have been dispensed and these were abstracted (Supplement 1). Dosage, route, and timing of hydroxychloroquine and azithromycin were collected. Chloroquine was originally planned for study, but the first 573 records screened indicated limited use (n = 9, 1.6%); patients receiving chloroquine were subsequently excluded from abstraction and analysis.

Outcomes

The primary outcome was in-hospital mortality, with additional secondary outcomes of cardiac arrest and abnormal electrocardiographic (ECG) findings (defined as arrhythmia or

prolonged QT fraction). Causes of death were coded by a study physician (J.K.) from open-text and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* fields. Adverse events examined were clinical evidence at any time during hospitalization of cardiac arrest or abnormal ECG findings (QT prolongation, other arrhythmias), as well as diarrhea and hypoglycemia.

Sample Size

An initial target sample size of 1500 was determined, assuming a 3:2 ratio of hydroxychloroquine use vs nonuse as was observed among the first 573 records received, previously observed mortality estimates, and α = .05.[16] This sample size was estimated to have 90% power to detect a significant hydroxychloroquine use vs nonuse mortality hazard ratio (HR) of 0.65, assuming 19% mortality among those not receiving hydroxychloroquine, and 95% power for HR of 0.50 when mortality was 10%. For adverse events with 10% prevalence among those not receiving hydroxychloroquine, power was 82% to detect a hydroxychloroquine use vs nonuse risk ratio (RR) of 1.5, and for events with 5% prevalence there was 95% power to detect an RR of 2.

Statistical Analysis

The distribution of treatment groups, including dose and timing, was summarized. Bivariate associations between treatment group and the measured patient characteristics were described and assessed with χ^2 tests for categorical variables and the Kruskal-Wallis test for continuous ones. We also assessed hospital outcomes and adverse events and their associations with patient characteristics.

A Cox proportional hazards model was fit for time to death, controlling for treatment group and potential confounders (age ≥65 years, sex, hospital, diabetes, chronic lung disease, cardiovascular disease [CVD, including hypertension, coronary artery disease, congestive heart failure], respiratory rate >22/min, O_2 saturation <90%, abnormal chest imaging findings, aspartate aminotransferase [AST]>40 U/L, and elevated creatinine levels) based on a priori plausibility, documented associations with death or hydroxychloroquine administration from previous studies, bivariate associations within our data, ruling out collinearity using condition indices, and missingness of less than 10%.[8,17-20]

We accounted for clustering within hospital using the robust sandwich estimator, with 2 sensitivity analyses considering control via stratification and random effects.[21] Comparisons were estimated for each medication group vs neither drug and for hydroxychloroquine alone vs azithromycin alone, with associations summarized with adjusted HR and direct-adjusted (ie, averaged across all observed patient covariate patterns) survival curves. The proportional hazards assumption for covariates was assessed, and was met, using weighted Schoenfeld residuals. A third sensitivity analysis was conducted that considered treatment as time-dependent, contributing pretreatment person-time to the neither drug group. Admission to the intensive care unit (ICU) and initiation of mechanical ventilation and treatment often happened quickly after hospital admission. This precluded meaningful time-to-event analyses of incident ICU admission or ventilation, and we focused efficacy analyses on in-hospital death.

The 2 primary adverse events of cardiac arrest and abnormal ECG findings were examined with generalized estimating equation logistic regression models, controlling for the same variables as in the mortality model. Repeated measures within hospital were accounted for using an exchangeable correlation structure and with robust variance estimation.

To understand the potential for an unmeasured confounder to render apparent significant ratio measures above 1.0 to be nonsignificant, when adjusted measures were found to be statistically significant we computed the E-value for the lower bound of the confidence interval.[22]

A sensitivity analysis stratified all end point models on receipt of mechanical ventilation. Models used a complete-case analysis approach. Analyses were completed in SAS version 9.4.

Significance was evaluated at α = .05 and all testing was 2-sided. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory.

Results

From a sample of 7914 patients with COVID-19 admitted in New York metropolitan hospitals during March 15 through 28, a total of 2362 records were randomly selected, and 1438 were abstracted and included in the analyses (Figure 1). The date of final follow-up was April 24, 2020. Of these patients, 735 (51.1%) received hydroxychloroquine + azithromycin, 271 (18.8%) received hydroxychloroquine alone, 211 (14.7%) received azithromycin alone, and 221 (15.4%) received neither drug.

Hydroxychloroquine was initiated at a median of 1 day (Q1-Q3, 1-2) following admission and azithromycin was given at a median of 0 days (Q1-Q3, 0-1). Additional information about dosing and administration appears in eTable 1 in Supplement 2. Nineteen patients initiated either medication prior to admission, including 12 who began medication use on the day prior, and another 3 began medication use 2 days prior to admission. Patients receiving neither drug also received few other abstracted medications; the most common were aspirin (38/192 [19.8%]) and lisinopril (13/193 [6.7%]) (eTable 2 in Supplement 2).

Patients receiving either drug were more likely (relative to neither drug) to be male (**Table 1**). Black or Hispanic patients were as likely to receive hydroxychloroquine and/or azithromycin. Median patient age was similar in the 4 groups (hydroxychloroquine + azithromycin, 61.4 years; hydroxychloroquine alone, 65.5 years; azithromycin alone, 62.5 years; and neither drug, 64.0 years [*P* = .35]). Six of 25 (24.0%) children received either hydroxychloroquine or azithromycin. Patients receiving hydroxychloroquine + azithromycin and hydroxychloroquine alone were more likely to be obese and have diabetes than those in the groups receiving azithromycin alone and neither drug. Patients receiving hydroxychloroquine alone had the highest levels of chronic lung disease (25.1%) and cardiovascular conditions (36.5%).

Table 1. Patient Characteristics by Treatment Group

	No./total No. (%)				
	Hydroxychloroquine + azithromycin (n = 735)	Hydroxychloroquine alone (n = 271)	Azithromycin alone (n = 211)	Neither drug (n = 221)	*P* value
Demographic characteristics					
Male sex	456 (62.0)	158 (58.3)	134 (63.5)	110 (49.8)	.006
Race/ethnicity					
White	167/694 (24.1)	40/256 (15.6)	53/204 (26.5)	61/214 (28.6)	.03
Black	199/694 (28.7)	76/256 (29.7)	46/204 (22.6)	50/214 (23.5)	
Hispanic	199/694 (28.7)	95/256 (37.1)	69/204 (33.8)	67/214 (31.5)	
Not listed above[a]	128/694 (18.5)	45/256 (17.6)	35/204 (17.2)	35/214 (16.4)	
Age, y					
<18	1 (0.1)	2 (0.7)	3 (1.4)	19 (8.6)	<.001
18-30	23 (3.1)	13 (4.8)	9 (4.3)	8 (3.6)	
31-44	105 (14.3)	29 (10.7)	29 (13.7)	34 (15.4)	
45-64	284 (38.6)	90 (33.2)	72 (34.1)	58 (26.2)	
≥65	322 (43.8)	137 (50.6)	98 (46.5)	102 (46.2)	
Preexisting conditions					
Smoking					
Current	25/547 (4.6)	7/194 (3.6)	7/170 (4.1)	6/163 (3.7)	.60
Former	100/547 (18.3)	47/194 (24.2)	32/170 (18.8)	27/163 (16.6)	
Never	422/547 (77.2)	140/194 (72.2)	131/170 (77.1)	130/163 (79.8)	
Obesity (BMI ≥30)	264/567 (46.6)	78/188 (41.5)	57/145 (39.3)	39/130 (30.0)	.005
Cancer	29 (4.0)	6 (2.2)	8 (3.8)	12 (5.4)	.32
Any kidney disease	88 (12.0)	47 (17.3)	21 (10.0)	31 (14.0)	.07
Any chronic lung conditions	129 (17.6)	68 (25.1)	38 (18.0)	24 (10.9)	<.001
Diabetes	269 (36.6)	113 (41.7)	58 (27.5)	64 (29.0)	.002
Any cardiovascular diseases	214 (29.1)	99 (36.5)	54 (25.6)	71 (32.1)	.04
Hypertension	426 (58.0)	162 (59.8)	107 (50.7)	121 (54.8)	.18
Coronary artery disease	93 (12.7)	37 (13.7)	18 (8.5)	25 (11.3)	.32
Congestive heart failure	46 (6.3)	29 (10.7)	10 (4.7)	11 (5.0)	.02
Dementia	35 (4.8)	19 (7.0)	16 (7.6)	23 (10.4)	.02
Clinical severity features within 24 h of admission					
Respiratory rate >22/min	178/706 (25.2)	43/247 (17.4)	26/203 (12.8)	36/198 (18.2)	<.001
Systolic BP <90 mm Hg or diastolic BP <60 mm Hg	76/709 (10.7)	30/247 (12.2)	21/204 (10.3)	24/194 (12.4)	.84
O_2 saturation, %					
<90	149/712 (20.9)	33/252 (13.1)	19/204 (9.3)	13/197 (6.6)	<.001
90-93	161/712 (22.6)	41/252 (16.3)	28/204 (13.7)	20/197 (10.2)	
>93	400/712 (56.5)	178/252 (70.6)	157/204 (77.0)	164/197 (83.3)	
Fever (temperature >38.0 °C)	261/710 (36.8)	98/246 (39.8)	67/204 (32.8)	55/198 (27.8)	.04
Elevated creatinine[b]	197/729 (27.0)	90/268 (33.6)	45/207 (21.7)	63/195 (32.3)	.02
AST >40 U/L	405/695 (58.3)	115/252 (45.6)	85/190 (44.7)	62/166 (37.4)	<.001
ALT >40 U/L	257/695 (37.0)	72/254 (28.4)	56/189 (29.6)	38/167 (22.8)	.001
Abnormal chest imaging findings[c]	698 (95.0)	240 (88.6)	173 (82.0)	122 (55.2)	<.001
COVID-19 diagnosis prior to admission	113/716 (15.8)	36/266 (13.5)	25/193 (13.0)	19/209 (9.1)	.10
Days prior to admission, median (IQR) [No.]	2 (1-4) [113]	3 (1-5) [36]	2 (1-3) [25]	4 (2-5) [19]	.38

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; BP, blood pressure; COVID-19, coronavirus disease 2019; IQR, interquartile range.

SI conversion factor: To convert creatinine to µmol/L, multiply values by 88.4.

[a] Including Asian/Pacific Islander, American Indian or Alaska Native, multiracial, and not specified.

[b] Elevated creatinine: >1.2 mg/dL for females, >1.4 mg/dL for males.

[c] Abnormal chest imaging was defined as having abnormal findings on x-ray, magnetic resonance imaging, and/or computed tomography scan at any point during hospitalization.

Table 2. Unadjusted Clinical Outcomes by Treatment Group

	No./total No. (%)			
	Hydroxychloroquine + azithromycin (n = 735)	Hydroxychloroquine alone (n = 271)	Azithromycin alone (n = 211)	Neither drug (n = 221)
ICU entry[a]	226 (30.7)	52 (19.2)	23 (10.9)	27 (12.2)
Within 0-1 d	126 (17.1)	22 (8.1)	18 (8.5)	18 (8.1)
>1 d	100 (13.6)	30 (11.1)	5 (2.4)	9 (4.1)
Mechanical ventilation	199 (27.1)	51 (18.8)	13 (6.2)	18 (8.1)
Within 0-1 d	98 (13.3)	16 (5.9)	11 (5.2)	11 (5.0)
>1 d	101 (13.7)	35 (12.9)	2 (0.9)	7 (3.2)
Before treatment initiation	55/733 (7.5)	9/268 (3.4)	1 (0.5)	
Concurrent with treatment initiation	48/733 (6.6)	8/268 (3.0)	7 (3.3)	
After treatment initiation	94/733 (12.8)	31/268 (11.6)	5 (2.4)	
Death (proportion of patients)	189 (25.7)	54 (19.9)	21 (10)	28 (12.7)
Among those not in the ICU or deceased within 0-1 d of admission	119/608 (19.6)	44/249 (17.7)	9/190 (4.7)	16/203 (7.9)
Cause of death[b]				
Known cause	118/189 (62.4)	38/54 (70.4)	17/21 (81)	20/28 (71.4)
Respiratory failure	82/118 (69.5)	26/38 (68.4)	11/17 (64.7)	13/20 (65.0)
Cardiac arrest	35/118 (29.7)	14/38 (36.8)	5/17 (29.4)	7/20 (35.0)
Pneumonia	27/118 (22.9)	5/38 (13.2)	2/17 (11.8)	3/20 (15.0)
COVID-19, unspecified	49/118 (41.5)	12/38 (31.6)	3/17 (17.7)	3/20 (15.0)
Sepsis	11/118 (9.3)	2/38 (5.3)	2/17 (11.8)	0/20 (0)
Other	18/118 (15.3)	4/38 (10.5)	2/17 (11.8)	3/20 (15.0)
Death (rate per patient-day)[c]	186/6241 (0.030)	54/2511 (0.022)	21/891 (0.024)	28/1257 (0.022)
After treatment initiation[c]	189/5151 (0.037)	54/2065 (0.026)	21/808 (0.026)	28/1257 (0.022)
Length of stay, median (IQR) [No.], d	7 (4-10) [735]	7 (4-12) [271]	3 (2-5) [211]	4 (2-7) [221]
Among those discharged	6 (4-10) [526]	6 (4-11) [200]	3 (2-5) [189]	3 (2-6) [186]
Among those still admitted	29 (27-33.5) [20]	28 (26-30) [17]	31 (NA) [1][d]	25 (21-26) [7]
Among those who died	7 (5-10) [189]	7 (5-11) [54]	4 (2-5) [21]	5.5 (2.5-8) [28]

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range.

[a] Receipt of intensive care may not have been in a traditional critical care unit.

[b] Based on open-text and *ICD-10* fields for cause of death. Causes are not mutually exclusive.

[c] Denominator is the total patient-days in the hospital experienced by the group.

[d] Not applicable (NA) because there was only 1 patient in this group still admitted at analysis.

As indicated by respiratory (chest imaging, respiratory rate, O_2 saturation) and hepatic (AST, alanine aminotransferase) measurements during the first 24 hours, patients in the treatment groups, particularly hydroxychloroquine + azithromycin, presented as having more clinically severe disease than the neither drug group. Ninety-five percent of the hydroxychloroquine + azithromycin group had abnormal chest imaging findings (top 3: air space opacity [63.0%], lung infiltrate [23.8%], and bronchopneumonia/pneumonia [20.7%]). No differences were observed in the timing of COVID-19 diagnosis; only 13.9% (193/1384) of patients were diagnosed before admission (median, 2 days before).

Bivariate analyses of patient characteristics and 3 outcomes of interest (mortality, cardiac arrest, and abnormal ECG findings) found that age of 65 years or older; history of cancer, kidney disease, cardiovascular conditions, and diabetes; abnormal chest imaging findings; O_2 saturation below 90%; low blood pressure; elevated creatinine levels; and elevated AST were significantly associated across outcomes (eTables 3, 4, and 5 in Supplement 2).

Hospital outcomes by treatment are presented in **Table 2**, noting 45 (3.1%) patients were still hospitalized at the time of final analysis. Patients receiving hydroxychloroquine + azithromycin (30.7%) and hydroxychloroquine alone (19.2%) had higher levels of ICU admission than those receiving azithromycin alone (10.9%) and neither drug (12.2%), although 56.1% of patients in all groups entered intensive care within 1 day of admission. Similarly, more patients receiving hydroxychloroquine + azithromycin (27.1%) and hydroxychloroquine alone (18.8%) than those taking azithromycin -alone (6.2%) and neither drug (8.1%) received mechanical ventilation. Among patients undergoing mechanical ventilation and receiving hydroxychloroquine + azithromycin, hydroxychloroquine alone, or azithromycin alone, 49.6% were ventilated before or concurrent with starting these treatments.

Primary Outcome

Overall in-hospital mortality was 20.3% (95% CI, 18.2%-22.4%). In unadjusted analyses, significant differences in in-hospital death were observed across the hydroxychloroquine + azithromycin (n = 189, 25.7% [95% CI, 22.3%-28.9%]), hydroxychloroquine alone (n = 54, 19.9% [95% CI, 15.2%-24.7%]), azithromycin alone (n = 21, 10.0% [95% CI, 5.9%-14.0%]), and neither-drug (n = 28, 12.7% [95% CI,

Table 3. Model-Adjusted Risk of In-Hospital Death, Cardiac Arrest, Arrhythmia

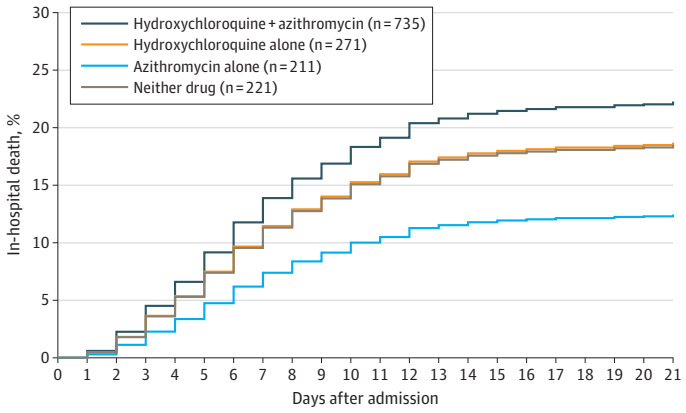
Outcome	Model type[a]	Estimate (95% CI)			
		Hydroxychloroquine + azithromycin vs neither drug	Hydroxychloroquine alone vs neither drug	Azithromycin alone vs neither drug	Hydroxychloroquine alone vs azithromycin alone
In-hospital death (hazard ratio)	Cox proportional hazards	1.35 (0.76-2.40)	1.08 (0.63-1.85)	0.56 (0.26-1.21)	1.92 (0.99-3.74)
Cardiac arrest (odds ratio)	GEE logistic regression	2.13 (1.12-4.05)	1.91 (0.96-3.81)	0.64 (0.27-1.56)	2.97 (1.56-5.64)
Abnormal ECG findings (odds ratio)[b]	GEE logistic regression	1.55 (0.89-2.67)	1.50 (0.88-2.58)	0.95 (0.47-1.94)	1.58 (0.77-3.24)

Abbreviations: ECG, electrocardiogram; GEE, generalized estimating equation.

[a] Models adjusted for sex, age category (<65 vs ≥65 years), diabetes, any chronic lung disease, cardiovascular disease, abnormal chest imaging, respiration rate >22/min, O_2 saturation <90%, elevated creatinine, and AST >40 U/L as fixed effects and repeated measures for hospital.

[b] Abnormal ECG included prolonged QT and arrhythmia.

Figure 2. Model-Adjusted Estimated In-Hospital Mortality, by Treatment Group



No. at risk (in hospital)

	Admission	Day 7	Day 14	Day 21
Hydroxychloroquine + azithromycin	735	653 (384)	568 (106)	557 (47)
Hydroxychloroquine alone	271	245 (136)	226 (59)	220 (28)
Azithromycin alone	211	191 (33)	190 (4)	190 (2)
Neither drug	221	206 (63)	197 (19)	195 (13)

Graph is based on a Cox proportional hazards model. Sample sizes provided reflect the source data observed, which informed the creation of the model. Compared with the neither-drug group, none of the 3 treatment groups had statistically different rates of death, at α = .05: hydroxychloroquine + azithromycin, P = .31; hydroxychloroquine alone, P = .79; and azithromycin alone, P = .14.

8.3%-17.1%]) groups (P < .001). Similar patterns were observed for death per patient-day overall and post drug initiation (Table 2).

In the primary analysis, following adjustment for demographics, specific hospital, preexisting conditions, and illness severity, no significant differences in mortality were found between patients receiving hydroxychloroquine + azithromycin (adjusted HR, 1.35 [95% CI, 0.76-2.40]), hydroxychloroquine alone (adjusted HR, 1.08 [95% CI, 0.63-1.85]), or azithromycin alone (adjusted HR, 0.56 [95% CI, 0.26-1.21]), compared with neither drug (**Table 3**) (complete case analysis variable completeness was 86%).

From this model, estimated direct-adjusted mortality at 21 days was 22.5% (95% CI, 19.7%-25.1%) with hydroxychloroquine + azithromycin, 18.9% (95% CI, 14.3%-23.2%) with hydroxychloroquine alone, 10.9% (95% CI, 5.8%-15.6%) with azithromycin alone, and 17.8% (95% CI, 11.1%-23.9%) with neither drug (**Figure 2**). No significant mortality difference was found between hydroxychloroquine alone and azithromycin alone (adjusted HR, 1.92 [95% CI, 0.99-3.74]). Results were similar in the 3 alternative Cox models (eTable 6 in Supplement 2).

Secondary Outcomes

Across all groups, the most commonly reported adverse event was abnormal ECG findings, particularly arrhythmia (**Table 4**). Abnormal ECG findings were more common among patients receiving hydroxychloroquine + azithromycin and hydroxychloroquine alone, both overall and among those with a record of ECG screening. However, in logistic regression models of abnormal ECG findings, there were no significant differences between the groups receiving neither drug and each of the hydroxychloroquine + azithromycin and hydroxychloroquine alone groups.

A greater proportion of patients receiving hydroxychloroquine + azithromycin experienced cardiac arrest (15.5%) and abnormal ECG findings (27.1%), as did those in the hydroxychloroquine alone group (13.7% and 27.3, respectively), compared with azithromycin alone (6.2% and 16.1%, respectively) and neither drug (6.8% and 14.0%, respectively). In adjusted models with those receiving neither drug as comparison, cardiac arrest was more likely in patients receiving hydroxychloroquine + azithromycin (adjusted OR, 2.13 [95% CI, 1.12-4.05]; E-value = 1.31), but not hydroxychloroquine alone (adjusted OR, 1.91 [95% CI, 0.96-3.81]) and azithromycin

Table 4. Adverse Events Reported During Hospitalization

	No./total No. (%)				
	Hydroxychloroquine + azithromycin (n = 735)	Hydroxychloroquine alone (n = 271)	Azithromycin alone (n = 211)	Neither drug (n = 221)	*P* value
Diarrhea	85 (11.6)	22 (17.0)	16 (8.5)	16 (7.2)	.003
Hypoglycemia	25 (3.4)	9 (3.3)	1 (0.5)	6 (2.7)	.15
Cardiac arrest	114 (15.5)	37 (13.7)	13 (6.2)	15 (6.8)	<.001
Abnormal ECG[a]					
Total sample	199 (27.1)	74 (27.3)	34 (16.1)	31 (14.0)	<.001
Among ECG screened	192/634 (30.3)	73/233 (31.3)	34/180 (18.9)	31/155 (20.2)	.002
Arrhythmia					
Overall	150 (20.4)	44 (16.2)	23 (10.9)	23 (10.4)	<.001
Among ECG screened	144/634 (22.7)	43/233 (18.5)	23/180 (12.8)	23/155 (14.8)	<.001
QT prolongation					
Overall	81 (11.0)	39 (14.4)	15 (7.1)	13 (5.9)	.006
Among ECG screened	80/634 (12.6)	39/233 (16.7)	15/180 (8.3)	3/155 (8.4)	.03

Abbreviation: ECG, electrocardiogram.

[a] Abnormal ECG combined arrhythmia and QT prolongation. Screening of adverse ECG at any point during hospitalization was reported in 634 (86.3%) of the hydroxychloroquine + azithromycin group, 233 (86.0%) of the hydroxychloroquine alone group, 180 (85.3%) of the azithromycin alone group, and 155 (70.1%) of the neither-drug group (χ^2 group differences, $P < .001$).

alone (adjusted OR, 0.64 [95% CI, 0.27-1.56]), and also in patients taking hydroxychloroquine alone vs azithromycin alone (adjusted OR, 2.97 [95% CI, 1.56-5.64]; E-value = 1.81).

In models for each outcome that stratified on receipt of mechanical ventilation, all associations were not significant, with the exception of cardiac arrest between patients receiving hydroxychloroquine alone vs azithromycin alone among patients who did not receive mechanical ventilation (adjusted OR, 3.01 [95% CI, 1.07-8.51]; E-value = 1.22) (eTable 7 in Supplement 2).

Discussion

In this study, during rapidly expanding hospitalization for COVID-19, 70% of patients received hydroxychloroquine alone or with azithromycin. Patients who received hydroxychloroquine with or without azithromycin were more likely (relative to patients receiving neither drug) to be male, have preexisting medical conditions, and have impaired respiratory or liver function at presentation. There were no significant differences in in-hospital mortality between patients who received hydroxychloroquine with or without azithromycin and patients who received neither drug.

The lack of observed benefit of hydroxychloroquine associated with in-hospital mortality, following adjustment for preexisting disease and severity of illness on admission, is consistent with recently reported data from other observational studies.[17,23,24]

To our knowledge, this study is the largest report of adverse effects of hydroxychloroquine among patients with COVID-19. Cardiac arrest was more frequent in patients who received hydroxychloroquine with azithromycin, compared with patients who received neither drug, even after adjustment. This is in the context of similar levels of preexisting coronary artery disease and hypertension, although patients receiving hydroxychloroquine with or without azithromycin were overall sicker on presentation.[25,26] Increased clinician vigilance for arrhythmias among patients receiving hydroxychloroquine may have led to a detection bias due to more frequent ECG performance. Given the lower association for arrhythmias than cardiac arrest, this may not have been a significant source of error. In the group of patients not receiving mechanical ventilation, risk for cardiac arrest remained statistically significantly elevated for hydroxychloroquine only compared with azithromycin only, suggesting that this risk was not mediated by mechanical ventilation.

The findings of this study also confirm what other studies have shown about the natural history of COVID-19 infection in the US: poor hospital outcomes were associated with male sex; preexisting conditions such as hypertension, obesity, and diabetes; and presenting findings such as elevated liver enzymes and abnormal kidney function.[18,27,28] These findings are comparable to other metropolitan New York single hospital-system COVID-19 patient case series,[18,27] but the design, which sampled from among 25 facilities representing 88.2% of the region's hospitalized patients, provides additional generalizability, given potential heterogeneity in hospital populations, protocols, and outcomes. There was no evidence in this study that black or Hispanic persons were prescribed these medications at a lower rate than white patients, which is relevant given the population-level differences in COVID-19 deaths previously reported by race and ethnicity.[29] The study sample likely included a small portion of patients from previous studies given overlapping observation periods and hospitals; however, data on hydroxychloroquine and azithromycin and associated outcomes have not been previously published.[18,27]

Strengths of this study include a large, random sample from 25 metropolitan New York hospitals. The sample was drawn early in the epidemic to include patients with long, complicated, and ongoing hospital stays.

Limitations

This study has several limitations. First, in sampling first hospitalizations, possible readmissions to other facilities may not be captured. Second, mortality was limited to in-hospital death, and patients discharged were assumed to still be alive during the study period. Third, some potential confounders such as inflammatory markers associated with severity of COVID-19 in prior studies were not frequently measured and thus not available for modeling.[18] Fourth, the rapidity with which patients entered the ICU and underwent mechanical ventilation, often concurrently with initiating hydroxychloroquine and azithromycin, rendered these outcomes unsuitable for efficacy analyses. Fifth, adverse events were collected as having occurred at any point during hospitalization, potentially before drug initiation, although both medications were started on average within 1 day of admission; future studies should examine the onset of these events relative to drug timing. Sixth, it is likely that there is unmeasured residual confounding due to factors not included in the analysis. For the significant associations of hydroxychloroquine + azithromycin vs no drug with cardiac arrest and hydroxychloroquine alone vs azithromycin alone with cardiac arrest, the respective E-values for the lower bound of the OR's CI of 1.31 and 1.81 suggest factors moderately associated with treatment and cardiac arrest could render these associations nonsignificant.[22] Seventh, for the subsample of 211 patients receiving azithromycin alone, the HR point estimate for mortality was 0.56, but the confidence interval crossed 1.0. This suggests the possibility of a true protective association, but it may also represent unmeasured confounding; it may warrant additional study. Eighth, the confidence intervals for some of the findings are wide, reflecting limits in study power for some analyses.

Clinical trials remain needed to provide definitive causal evidence of the effect of hydroxychloroquine and azithromycin on mortality, while also providing an opportunity to more finely control baseline patient severity and the dose and timing of drug administration. Nonetheless, the findings of the present study should be considered in concert with recent COVID-19 treatment guidelines from the National Institutes of Health and Infectious Diseases Society of America as well as the statement regarding safety concerning use of hydroxychloroquine from the US Food and Drug Administration.[30-32]

Conclusions

Among patients hospitalized in metropolitan New York with COVID-19, treatment with hydroxychloroquine, azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality. However, the interpretation of these findings may be limited by the observational design.

ARTICLE INFORMATION

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Concept and design: Rosenberg, Dufort, Udo, Wilberschied, Kumar, Kirkwood, DeHovitz, Blog, Hutton, Holtgrave, Zucker.
Acquisition, analysis, or interpretation of data: Rosenberg, Dufort, Udo, Wilberschied, Kumar, Tesoriero, Weinberg, Kirkwood, Muse, DeHovitz, Blog, Holtgrave.
Drafting of the manuscript: Rosenberg, Dufort, Udo, Wilberschied, Kumar, Blog, Holtgrave.
Critical revision of the manuscript for important intellectual content: Rosenberg, Dufort, Udo, Wilberschied, Kumar, Tesoriero, Weinberg, Kirkwood, Muse, DeHovitz, Hutton, Holtgrave, Zucker.
Statistical analysis: Rosenberg, Udo, Wilberschied, Kumar, Holtgrave.
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