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Title: **Examination of Changes in Patient Characteristics and Hydroxychloroquine use based on U.S. Food and Drug Administration's Recommendation**

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Abstract (299/300 words)

Objective: To examine the association between hydroxychloroquine use and clinical outcomes arising from changes in the U.S. Food and Drug Administration (FDA)'s recommendation and changes in patient characteristics in each period.

Design: A retrospective cross-sectional analysis.

Setting and Participants: We included hospitalized adult patients with confirmed COVID-19 infections from 12 Northwell Health acute care hospitals between March 1, 2020 and May 11, 2020. We categorized changes in the FDA recommendation as pre-FDA approval (March 1, 2020-March 27, 2020), FDA approval (March 28, 2020-April 23, 2020), and FDA warning (April 24, 2020-May 11, 2020). The hydroxychloroquine treated group received at least one dose within 48 hours of hospital admission.

Primary outcome: A composite of intubation and inpatient death.

Results: The percentages of patients who were treated with hydroxychloroquine were 192/2202 (8.7%) pre-FDA approval, 2902/6741 (43.0%) FDA approval, and 176 (16.5%) FDA warning period (p-value<0.001). Using propensity score-matching, there was a higher rate of the composite outcome among patients treated with hydroxychloroquine (49/192, 25.5%) compared to no hydroxychloroquine (66/384, 17.2%) in the pre-FDA approval period (p-value=0.03) but not in the FDA-approval period (25.5% vs 22.6%, p=0.08) or the FDA warning (21.0% vs 15.1%, p=0.11) periods. Coincidently, there was an increase in number of COVID-19 patients and disease severity during the FDA approval period (24.1% during FDA approval versus 21.4% during pre-FDA approval period). Hydroxychloroquine use was associated with increased odds of the composite outcome during the pre-FDA approval period (OR=1.65 [1.09-2.51]) but not

during the FDA approval (OR=1.17 [0.99-1.39]) and FDA warning (OR=1.50 [0.94-2.39]) periods.

Conclusions: There were concurrent changes in percentage of COVID-19 patients treated with hydroxychloroquine and the number (and disease severity) of hospitalized patients with COVID-19 infections. Adverse clinical outcomes were significantly associated with hydroxychloroquine use only during pre-FDA approval period but not during FDA-approval and warning periods.

Article Summary

- The percentages of patients who were treated with hydroxychloroquine were 192/2202 (8.7%) pre-FDA approval, 2902/6741 (43.0%) FDA approval, and 176 (16.5%) FDA warning period (p-value<0.001).
- Using propensity score-matching, there was a higher rate of the composite outcome of intubation and inpatient mortality among patients treated with hydroxychloroquine compared to no hydroxychloroquine in the pre-FDA approval period but not in the FDA-approval period or the FDA warning periods.
- Hydroxychloroquine use was associated with increased odds of the composite outcome during the pre-FDA approval period but not during the FDA approval and FDA warning periods.

Introduction

Coronavirus Disease 2019 (COVID-19), which causes severe acute respiratory syndrome, has spread globally. One consequence has been the unprecedented number of intensive care unit (ICU) admissions requiring mechanical ventilation. The mortality of patients on mechanical ventilation has been reported to be 60-80% with an overall hospital mortality of 20-25%.[1,2] As of June 10, 2020, over 7.3 million people have been infected with COVID-19 and 410,000 deaths have been reported globally.[3] Although multiple vaccines are in preparation or have begun clinical testing, data on safety and efficacy required to immunize the general public is currently unavailable and may be months to years away. Therefore, the need to identify medications that are associated with slowed COVID-19 progression or decreased mortality remains urgent.

Hydroxychloroquine, a medication commonly used to prevent malaria infection and treat autoimmune diseases, has been found to be effective in treating COVID-19 *in vitro*.[4-9] Hydroxychloroquine is found to reduce the entry of coronavirus into a cell through interference with the terminal glycosylation of angiotensin-converting enzyme 2 receptor, which inhibits viral replication.[4,6] Additionally, hydroxychloroquine has immunomodulatory activity, and may inhibit cytokine production and prevent the occurrence of cytokine storm.[10] Early evidence suggests that hydroxychloroquine can serve as a potential treatment for COVID-19.[11-13] However, tecent studies examining treatment of COVID-19 with hydroxychloroquine showed mixed results, with some studies showing no average benefit in outcomes, including intubation or inpatient mortality, but other studies showed worse outcomes.[14-18]

However, no study has accounted for how changes in recommendations for hydroxychloroquine by the United States Food and Drug Administration (FDA) affected outcomes of patients treated for COVID-19. On March 28, 2020, the FDA issued an Emergency

Use Authorization for hydroxychloroquine in the treatment of COVID-19 infection. During this time, there was also an increased number of hospitalized patients with COVID-19, which may have resulted in changes in hospital capacity and disease severity.[3] Subsequently, on April 24, 2020, the FDA cautioned against using hydroxychloroquine for COVID-19 infection.[19] These changes in the recommendation of hydroxychloroquine as a treatment for COVID-19 infection may have impacted whether patients were treated with hydroxychloroquine for COVID-19. These two events occurring concurrently could affect the association of hydroxychloroquine with COVID-19 outcomes. Therefore, we used data from one of the largest healthcare systems in the United States and examined the association between hydroxychloroquine use and patients' clinical outcomes based on changes in FDA recommendation.

Methods

Setting

We used data from Northwell Health, the largest academic healthcare system in New York. Northwell Health serves approximately 11 million patients throughout Long Island, New York City, and Westchester County and has 23 affiliated healthcare facilities, including 12 acute care hospitals. The Institutional Review Board for the Feinstein Institutes for Medical Research at Northwell Health approved this case series as minimal-risk research using data collected for routine clinical practice and waived the requirement for informed consent.

Data Source

Data for this study was obtained from the enterprise's inpatient electronic health record (EHR; Sunrise Clinical Manager, Allscripts, Chicago, IL), which covers 12 of Northwell Health's hospitals.

Study Population

The study population included all adult patients (n=13,258), aged 18 years and older, hospitalized at one of Northwell Health's 12 acute care hospitals between March 1, 2020 and May 11, 2020 with a diagnosis of COVID-19 confirmed by a positive result on polymerase chain reaction testing of a nasopharyngeal sample. For patients with multiple COVID-19 tests, they were considered to have a confirmed COVID-19 infection if any of the repeated tests within the same hospitalization returned positive. We excluded patients who died or were intubated within one day of hospitalization because their clinical outcomes were likely predetermined by pre-hospitalization factors. We also excluded patients who were discharged within one day of admission. Patients who were admitted to the obstetrics service were excluded as all obstetrics patients were screened for COVID-19 on their admission. For patients with multiple hospitalizations for COVID-19, we used their first hospitalization with a confirmed diagnosis of COVID-19. We excluded 3,249 patients who did not meet the inclusion and exclusion criteria.

Exposure

Patients were identified as treated with hydroxychloroquine if they received at least one dose within 48 hours of admission. The control group for this analysis consisted of patients who were not treated with hydroxychloroquine within 48 hours of admission. Patients who did not initially receive hydroxychloroquine within 48 hours but received the medication later in their

hospitalization were kept in the control group. We excluded COVID-19 patients who were treated with azithromycin or a combination of hydroxychloroquine and azithromycin. We also excluded patients who were intubated prior to getting their first dose of hydroxychloroquine within 48 hours of admission.

Outcomes

The primary outcome of interest was a composite outcome of the earlier of time to intubation or time to inpatient death. Time until composite event was censored at time of discharge for patients who were discharged alive with no intubation during their hospitalization. The rationale for the combined primary outcome was twofold: 1) many patients who deteriorated clinically died without being intubated, often due to transition to palliative care; and 2) hospitalization stays for intubated COVID-19 patients have been very long, and many intubated COVID-19 patients at the time of the analyses may not ultimately survive. For a sensitivity analysis, we used death as the outcome. We tracked all patients who were not discharged or died until June 1, 2020.

Covariates

We collected data on patients' demographic characteristics and comorbidities. Demographic characteristics included age, sex, race/ethnicity, and health insurance (commercial, Medicaid, Medicare, other, and no insurance). We used patient-reported race and ethnicity information and categorized patients into one of five racial/ethnic groups: White, Black, Asian, Other/Multiracial, and Unknown/Declined. We also identified a subgroup of patients who received immunomodulatory medications, including steroids (prednisone or

methylprednisolone), sarilumab, tocilizumab, anakinra, or colchicine, and included this information as a covariate. We identified the presence of the following comorbidities by *International Statistical Classification of Disease and Relate Health Problems, Tenth Revision (ICD-10)* coding: cancer, coronary artery disease, hypertension, asthma, chronic obstructive pulmonary disease, diabetes, chronic liver disease, chronic kidney disease, and end stage renal disease. We calculated the Charlson Comorbidity Index, which is an index that predicts the 10-year survival of patients with multiple comorbidities, as a measure of total comorbidity burden.[20] The only covariate with missing data was BMI, and we categorized the BMI group as not obese (BMI less than 30kg/m^2), obese (BMI greater than or equal to 30kg/m^2), and missing BMI.

We categorized changes in FDA recommendation for hydroxychloroquine, into three time periods: 1) pre-FDA approval (March 1-March 27, 2020); 2) FDA approval (March 28-April 23, 2020); and 3) FDA warning (April 24-May 11, 2020).

Statistical analysis

All analyses were performed using version 3.5.2 of the R Programming Language (R Project for Statistical Computing, R Foundation, Vienna, Austria). We first performed chi-square and 2-sample t-tests to compare patient characteristics treated with hydroxychloroquine to no hydroxychloroquine (control).

We used propensity-score matching methods, 1:2 for the pre-FDA approval and the FDA warning periods and 1:1 for the FDA approval period, using the smaller group as a reference, within each period and applied the nearest-neighbor method to create a matched control sample. The propensity-score matching was performed within each period so that patients admitted

within the FDA approval period were not matched to patients in the pre-FDA approval or FDA warning periods, so as not to confound the effect of different FDA recommendations.

We then took the following approach to conduct the analysis. We first performed logistic regressions to compare the propensity score-matched hydroxychloroquine group to the control group. For a time-to-event analysis, we used the Kaplan-Meier survival estimate and log-rank test We examined the Kaplan-Meier survival curves for the treatment group compared to the control group, separated by the different FDA recommendation periods. If a patient was discharged alive without intubation, data was censored at the time of hospital discharge. Then, we used Cox proportional-hazard regression models to estimate the association between the propensity-matched treatment group to the control group with respect to end point free survival time. We used the Schoenfeld residuals to test the proportional hazard assumption in the Cox model.

Results

Characteristics of the cohort

From a cohort of 10,009 patients, 3,270 (32.7%) were treated with hydroxychloroquine, 2,640 (26.4%) with neither hydroxychloroquine nor azithromycin, 1,289 (12.9%) with azithromycin only, and 2,810 (28.1%) with the combination hydroxychloroquine and azithromycin. There were differences in the number of patients treated with or without hydroxychloroquine and/or azithromycin by admission period (Figure 1).

We found significant differences in the use of hydroxychloroquine and patient characteristics based on changes to FDA recommendation. Number and percentages of patients treated with hydroxychloroquine were 192/2202 (8.7%) pre-FDA approval, 2902/6741 (43.0%)

during FDA approval, and 176 (16.5%) during the FDA warning period (p-value<0.001). There was a significant increase in number of patients during the FDA approval period (March 28-April 23). During the pre-FDA approval period, there were 2,202 patients admitted with COVID-19 infection, but in the following periods, the number of patients admitted with COVID-19 infections was 6,741 (FDA approval period) and 1,066 (FDA warning period). Throughout the study, and independent of FDA periods, there were differences in sociodemographic and clinical characteristics between the treatment group compared to the control group (Table 1). Higher percentage of patients who were younger (36.8% vs 32.5% were less than 60 years old), male (59.9% vs 53.4%), and had commercial insurance (31.0% vs 24.2%) were treated with hydroxychloroquine (p-values<0.001). Presence of comorbidity was associated with hydroxychloroquine use (all p-values<0.05), except for asthma and diabetes, and chronic kidney disease.

Hydroxychloroquine groups (13.4%) had higher rates of intubation compared to the control group (7.0%) (p-value<0.001). Inpatient mortality was 20.2% for hydroxychloroquine versus 18.3% for no hydroxychloroquine treatment (p-value=0.01). A significantly higher percentage of patients treated with hydroxychloroquine (23.4%) reached the composite outcome compared to the control group (20.4%) (p-value=0.007). A higher percentage of patients on hydroxychloroquine (52.8%) were treated concurrently with immunomodulatory medications compared to the control group (24.7%) (p-value<0.001).

After propensity-score matching within each time period, sociodemographic characteristics and comorbidity were similar between hydroxychloroquine and no hydroxychloroquine group (Table 2). There were 576 patients in the pre-FDA approval period, 2812 patients in the FDA approval period, and 528 FDA warning period. There was a higher

composite outcome among patients treated with hydroxychloroquine (25.5%) compared to no hydroxychloroquine (17.2%) during the pre-FDA approval period (p-value=0.03) but no difference in the number of composite outcomes between hydroxychloroquine and no hydroxychloroquine groups in the FDA-approval period (25.5%, vs 22.6% p=0.08) or the FDA warning period (21.0 vs 15.1% %, p=0.11) (Table 3). In multivariable logistic regression analysis, hydroxychloroquine use was associated with increased odds of the composite outcome during the pre-FDA approval period (OR=1.65 [1.09-2.51]) but there was no association during the FDA approval (OR=1.17 [0.99-1.39]) as well as the FDA warning period (OR=1.50 [0.94-2.39]).

Time-to event analysis

Figure 2 shows the Kaplan-Meier curves of freedom from the composite end point of intubation and inpatient mortality during the pre-FDA approval period, the FDA approval period, or the FDA warning period. The cox proportional-hazard regression models showed hydroxychloroquine use was associated with the composite outcome of intubation and inpatient mortality during the pre-FDA approval (hazard ratio=1.70 [1.17-2.48]) and the FDA warning (hazard ratio=1.53 [1.00-2.34]) period but not during the FDA approval period (hazard ratio=1.03 [0.88-1.20]) (Table 3).

Discussion

In our study, while there were changes in percentage of COVID-19 patients treated with hydroxychloroquine with FDA recommendations, there was also a fluctuation of the number of

hospitalized patients with COVID-19 infections during the FDA approval period. Hydroxychloroquine treatment was associated with increased composite outcome of intubation or death during pre-FDA approval period but not during FDA approval or FDA warning period. The overall association of hydroxychloroquine treatment among COVID-19 patients in our cohort was similar to previous studies showing no association between the treatment and primary end point of intubation or death.[14,15]

Although not captured in our study, hospitals during the FDA approval period had to manage sudden increases in critically ill patients. As hospitals were reaching their maximum capacity, coordinated efforts were made to ensure that there were adequate ventilators for patients with pulmonary complications, goals of care discussions for patients with poor prognosis, and an increase in ambulatory management to ensure medical care for all patients.[21-23] Therefore, patients who were admitted during this period may have had more severe disease, including hypoxia, requiring ventilators. This hypothesis is also consistent with the higher proportions of patients experiencing the composite outcome during this period. There was also an increased use of immunomodulators, which were more often used for patients with more complications, including acute respiratory distress syndrome, acute kidney injury, thrombosis, etc.[1,24,25] Therefore, regardless of whether they were being treated with hydroxychloroquine or not, patients admitted during the FDA approval period had overall worse outcomes compared to patients admitted during other periods. Because of such differences in patient disease severity and hospital settings, we used propensity-score matching of patients within each period so that the patients treated in the pre-FDA approval or FDA warning periods were not matched with patients treated in the FDA approval period.

The lack of efficacy of hydroxychloroquine could be attributed to the severity of disease among patients receiving medication. The hypothesized mechanism of action of hydroxychloroquine is that it prevents the virus from entering cells and blocks viral replication.[4-6] These patients were hospitalized because of a severe course of disease, and therefore it is likely that viral replication was already high when hydroxychloroquine was administered. This may be particularly true for patients who were hospitalized during the FDA approved period because hospitals had a high number of COVID-19 patients requiring inpatient care. Also, hydroxychloroquine may have been administered to more severely ill patients and subsequently was associated with higher risk of intubation and/or inpatient mortality. We addressed this by propensity-score matching patients treated with hydroxychloroquine to no hydroxychloroquine. Of note, higher doses of hydroxychloroquine have been associated with adverse intermediate outcomes, including QTc prolongation, in another study.[26]

This study has several limitations. Due to the observational study design, this study does not establish causal relationships between medication treatment and outcomes. Also, this study is limited to the inpatient setting, therefore the study findings are not generalizable to outpatient or community settings. Though we did attempt to adjust for covariates, it is possible that the severity of illness and precise timing of treatment also may have influenced the association of these medications with the outcome. There might be a subset of patients who were taking hydroxychloroquine prescribed by their ambulatory providers prior to their hospitalization. It is possible that some patients in the no hydroxychloroquine group were taking the medications or already had completed their 5-day course prior to hospitalization. There was a subset of patients in the control group who were treated with hydroxychloroquine or azithromycin after 48 hours because of their disease progression. The changes in the FDA recommendations probably also

caused some patients admitted during the pre-FDA approval period to be treated with hydroxychloroquine during their prolonged hospitalizations. This could result in bias toward the null, that is, erroneously concluding no difference between hydroxychloroquine and control (Type II error).

In addition to changes in the FDA recommendation, this study addresses changes in case mix due to changes in number of COVID-19 patients being hospitalized. Regardless of FDA recommendation for the drug, we did not observe any beneficial association of hydroxychloroquine use throughout the study period. This study suggests that hydroxychloroquine may not alter the clinical course among patients with COVID-19 infections in the inpatient setting where patients have more severe disease. However, it is unclear whether hydroxychloroquine treatment can be used in patients with milder symptoms and possibly in an outpatient setting. On June 15, 2020, the FDA revoked the Emergency Use Authorization for hydroxychloroquine in the treatment of COVID-19 infection and this will further decrease the number of COVID-19 patients being treated with hydroxychloroquine.[27] These study results should not be used as guidance on whether or not to treat COVID-19 patients with or without hydroxychloroquine due to its observational design.

Data Availability Statement

The data that support the findings of this study are available on request from COVID19@northwell.edu. The data are not publicly available due to restrictions as it could compromise the privacy of research participants.

Conflict of Interest Disclosures

The authors report no real or apparent conflicts of interest.

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The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The views expressed in this paper are those of the authors and do not represent the views of the National Institutes of Health, the United States Department of Health and Human Services, or any other government entity.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

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Table 1. Patient characteristics before propensity-score matching, number (percentage) for categorical variable and mean (standard deviation) for continuous variable

	All (n=10,009)	HCQ (n=3,270)	No HCQ (n=2,640)	P-value*
Sociodemographic characteristics				
Age at admission, mean (SD)	64.99 (16.35)	64.29 (15.58)	66.87 (17.73)	<0.001
Age group				<0.001
18-49	1747 (17.5)	558 (17.1)	434 (16.4)	
50-59	1863 (18.6)	645 (19.7)	425 (16.1)	
60-69	2277 (22.7)	816 (25.0)	530 (20.1)	
70-79	2046 (20.4)	671 (20.5)	518 (19.6)	
80+	2076 (20.7)	580 (17.7)	733 (27.8)	
Male	5847 (58.4)	1959 (59.9)	1411 (53.4)	<0.001
Race				<0.001
White	3923 (39.2)	1151 (35.2)	1182 (44.8)	
Black	2104 (21.0)	632 (19.3)	581 (22.0)	
Asian	849 (8.5)	327 (10.0)	236 (8.9)	
Other/Multiracial	2648 (26.5)	958 (29.3)	540 (20.5)	
Unknown	485 (4.8)	202 (6.2)	101 (3.8)	
Health insurance				<0.001
Commercial	2947 (29.4)	1013 (31.0)	638 (24.2)	
Medicaid	2041 (20.4)	712 (21.8)	488 (18.5)	
Medicare	4754 (47.5)	1431 (43.8)	1453 (55.0)	
Other	133 (1.3)	46 (1.4)	45 (1.7)	
No insurance	134 (1.3)	68 (2.1)	16 (0.6)	
Comorbidity				
Cancer	832 (8.3)	238 (7.3)	278 (10.5)	<0.001
Coronary artery disease	1339 (13.4)	399 (12.2)	429 (16.2)	<0.001
Hypertension	6073 (60.7)	1973 (60.3)	1673 (63.4)	0.02
Peripheral artery/vascular disease	282 (2.8)	81 (2.5)	100 (3.8)	0.005
Asthma	842 (8.4)	271 (8.3)	198 (7.5)	0.29
Chronic obstructive pulmonary disease	639 (6.4)	168 (5.1)	174 (6.6)	0.02
Diabetes	3624 (36.2)	1233 (37.7)	945 (35.8)	0.14
Chronic liver disease	298 (3.0)	74 (2.3)	110 (4.2)	<0.001
Chronic kidney disease	507 (5.1)	155 (4.7)	152 (5.8)	0.09
End stage renal disease	461 (4.6)	144 (4.4)	168 (6.4)	0.001
Charlson Comorbidity Index, mean SD	4.89 (3.58)	4.56 (3.38)	5.74 (3.77)	<0.001
Obesity				<0.001
Obese	2810 (28.1)	1001 (30.6)	570 (21.6)	
Not obese	4632 (46.3)	1483 (45.4)	1296 (49.1)	
Missing BMI	2567 (25.6)	786 (24.0)	774 (29.3)	
BMI, mean (SD)	29.23 (7.06)	29.66 (7.04)	28.13 (7.14)	<0.001

Clinical outcomes				
Admission week				<0.001
Pre-FDA approval	2202 (22.0)	192 (5.9)	496 (18.8)	
FDA approval	6741 (67.3)	2902 (88.7)	1406 (53.3)	
FDA warning	1066 (10.7)	176 (5.4)	738 (28.0)	
Length of stay, mean (SD)	9.51 (9.60)	9.56 (9.14)	8.80 (9.27)	0.001
Immunomodulator use	4183 (41.8)	1727 (52.8)	651 (24.7)	<0.001
ICU stay	1985 (19.8)	583 (17.8)	426 (16.1)	0.09
Mechanical ventilation	1314 (13.1)	437 (13.4)	186 (7.0)	<0.001
Inpatient mortality	1983 (19.8)	660 (20.2)	482 (18.3)	0.01
Composite Outcome	2413 (24.1)	764 (23.4)	538 (20.4)	0.007

* Comparing hydroxychloroquine group to no treatment group

Table 2. Patient characteristics after propensity-score matching, number (percentage) for categorical variable and mean (standard deviation) for continuous variable

	Pre-FDA approval				FDA approval				FDA warning			
	HCQ (n=192)	No HCQ (n=384)	P-value*	SMD	HCQ (n=1406)	No HCQ (n=1406)	P-value*	SMD	HCQ (n=176)	No HCQ (n=352)	P-value*	SMD
Sociodemographic characteristics												
Age at admission, mean (SD)	61.1 (15.8)	62.8 (17.2)	0.26	0.101	67.8 (15.8)	67.3 (17.6)	0.42	0.03	66.2 (16.2)	66.3 (17.6)	0.94	0.007
Male	109 (56.8)	218 (56.8)	1.00	<0.001	740 (52.6)	765 (54.4)	0.36	0.036	92 (52.3)	194 (55.1)	0.60	0.057
Race			0.68	0.134			1.00	0.013			0.99	0.05
White	91 (47.4)	180 (46.9)			610 (43.4)	612 (43.5)			65 (36.9)	136 (38.6)		
Black	35 (18.2)	86 (22.4)			306 (21.8)	302 (21.5)			37 (21.0)	69 (19.6)		
Asian	17 (8.9)	37 (9.6)			143 (10.2)	143 (10.2)			12 (6.8)	25 (7.1)		
Other/Multiracial	44 (22.9)	72 (18.8)			297 (21.1)	296 (21.1)			53 (30.1)	106 (30.1)		
Unknown	5 (2.6)	9 (2.3)			50 (3.6)	53 (3.8)			9 (5.1)	16 (4.5)		
Health insurance			0.02	0.257			0.90	0.039			1.00	0.036
Commercial	91 (47.4)	134 (34.9)			306 (21.8)	321 (22.8)			44 (25.0)	92 (26.1)		
Medicaid	30 (15.6)	72 (18.8)			246 (17.5)	249 (17.7)			31 17.6)	62 (17.6)		
Medicare	71 (37.0)	178 (46.4)			819 (58.3)	805 (57.3)			92 (52.3)	182 (51.7)		
Other	0 (0.0)	0 (0.0)			27 (1.9)	22 (1.6)			6 (3.4)	11 (3.1)		
No insurance	0 (0.0)	0 (0.0)			8 (0.6)	9 (0.6)			3 (1.7)	5 (1.4)		
Comorbidity												
Cancer	10 (5.2)	25 (6.5)	0.67	0.055	134 (9.5)	151 (10.7)	0.32	0.04	16 (9.1)	30 (8.5)	0.96	0.02
Coronary artery disease	23 (12.0)	56 (14.6)	0.47	0.077	218 (15.5)	222 (15.8)	0.88	0.008	27 (15.3)	53 (15.1)	1.00	0.008
Hypertension	109 (56.8)	237 (61.7)	0.29	0.101	915 (65.1)	884 (62.9)	0.24	0.046	107 (60.8)	205 (58.2)	0.64	0.052
Peripheral artery/vascular disease	7 (3.6)	13 (3.4)	1.00	0.014	48 (3.4)	42 (3.0)	0.59	0.024	6 (3.4)	6 (1.7)	0.35	0.108
Asthma	24 (12.5)	35 (9.1)	0.26	0.109	88 (6.3)	100 (7.1)	0.41	0.034	17 (9.7)	32 (9.1)	0.96	0.019
Chronic obstructive pulmonary disease	9 (4.7)	23 (6.0)	0.65	0.058	83 (5.9)	87 (6.2)	0.81	0.012	14 (8.0)	29 (8.2)	1.00	0.01
Diabetes	70 (36.5)	138 (35.9)	0.98	0.011	515 (36.6)	508 (36.1)	0.81	0.01	68 (38.6)	131 (37.2)	0.82	0.029
Chronic liver disease	7 (3.6)	15 (3.9)	1.00	0.014	47 (3.3)	56 (4.0)	0.42	0.034	7 (4.0)	19 (5.4)	0.62	0.067
Chronic kidney disease	11 (5.7)	25 (6.5)	0.86	0.033	84 (6.0)	80 (5.7)	0.81	0.012	8 (4.5)	17 (4.8)	1.00	0.013

End stage renal disease	12 (6.2)	27 (7.0)	0.86	0.031	99 (7.0)	101 (7.2)	0.94	0.006	4 (2.3)	8 (2.3)	1.00	<0.001
Charlson Comorbidity Index, mean SD	4.23 (3.19)	4.73 (3.32)	0.09	0.152	5.72 (3.75)	5.69 (3.73)	0.84	0.008	5.03 (3.23)	5.01 (3.42)	0.96	0.005
Obesity			0.08	0.198			0.84	0.022			0.96	0.027
Obese	76 (39.6)	116 (30.2)			289 (20.6)	292 (20.8)			50 (28.4)	98 (27.8)		
Not obese	69 (35.9)	160 (41.7)			678 (48.2)	663 (47.2)			84 (47.7)	166 (47.2)		
Missing BMI	47 (24.5)	108 (28.1)			439 (31.2)	451 (32.1)			42 (23.9)	88 (25.0)		
Clinical outcomes												
Length of stay, mean (SD)	10.88 (11.20)	10.48 (11.79)	0.70	0.035	9.29 (8.66)	7.75 (7.82)	<0.001	0.187	8.67 (7.55)	8.28 (7.40)	0.57	0.053
Mechanical ventilation	33 (17.2)	29 (7.6)	0.001	0.296	168 (11.9)	85 (6.0)	<0.001	0.207	26 (14.8)	25 (7.1)	0.008	0.248
Inpatient mortality	31 (16.1)	55 (14.3)	0.32	0.272	318 (22.6)	294 (20.9)	0.32	0.086	32 (18.2)	46 (13.1)	1.00	0.079
Composite Outcome	49 (25.5)	66 (17.2)	0.03	0.204	359 (25.5)	318 (22.6)	0.08	0.068	37 (21.0)	53 (15.1)	0.11	0.156

* Comparing hydroxychloroquine group to no treatment group
SMD=Standardized mean difference

Table 3. Association between hydroxychloroquine use and the composite end point in the crude analysis and propensity-score matched analysis

Analysis	Results	P-value*
Composite outcome among patients at risk, n (%)		
Before propensity score matching		
All periods		
Overall	2080/10009 (23.9)	-
Hydroxychloroquine	764/3270 (23.4)	0.007
No HCQ	538/2640 (20.4)	
After propensity score matching		
Pre-FDA approval		
Hydroxychloroquine	49/192 (25.5)	0.03
No HCQ	66/384 (17.2)	
FDA approval		
Hydroxychloroquine	359/1406 (25.5)	0.08
No HCQ	318/1406 (22.6)	
FDA warning		
Hydroxychloroquine	37/176 (21.0)	0.11
No HCQ	53/352 (15.1)	
Multivariable analysis - odds ratio [95% confidence interval]*		
Pre-FDA approval (reference: no HCQ)	1.65 [1.09-2.51]	0.02
FDA approval (reference: no HCQ)	1.17 [0.99-1.39]	0.07
FDA warning (reference: no HCQ)	1.50 [0.94-2.39]	0.09
Propensity-score matched analyses-hazard ratio [95% confidence interval]*		
Pre-FDA approval (reference: no HCQ)	1.70 [1.17-2.48]	0.005
FDA approval (reference: no HCQ)	1.03 [0.88-1.20]	0.72
FDA warning (reference: no HCQ)	1.53 [1.00-2.34]	0.05

* Comparing hydroxychloroquine group to no treatment group

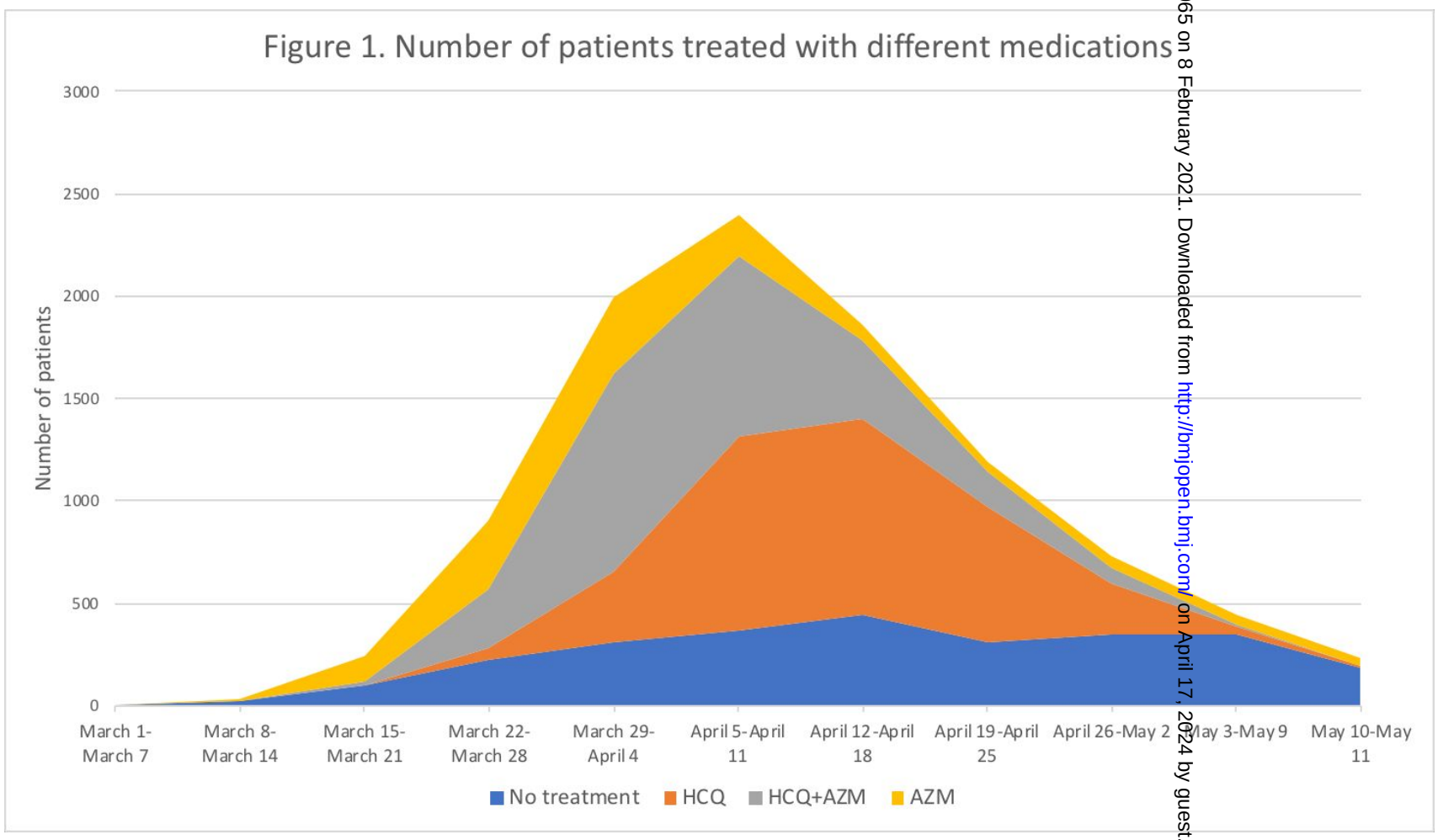
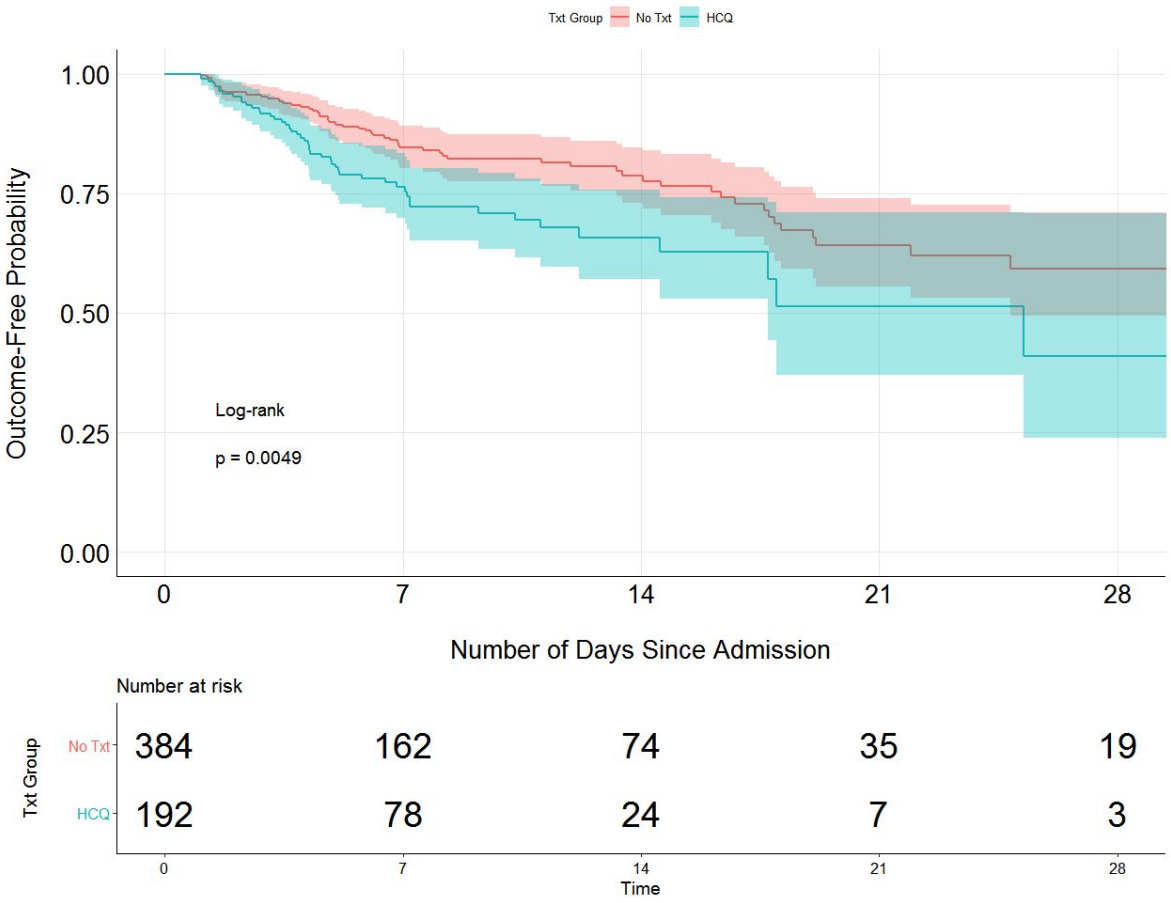
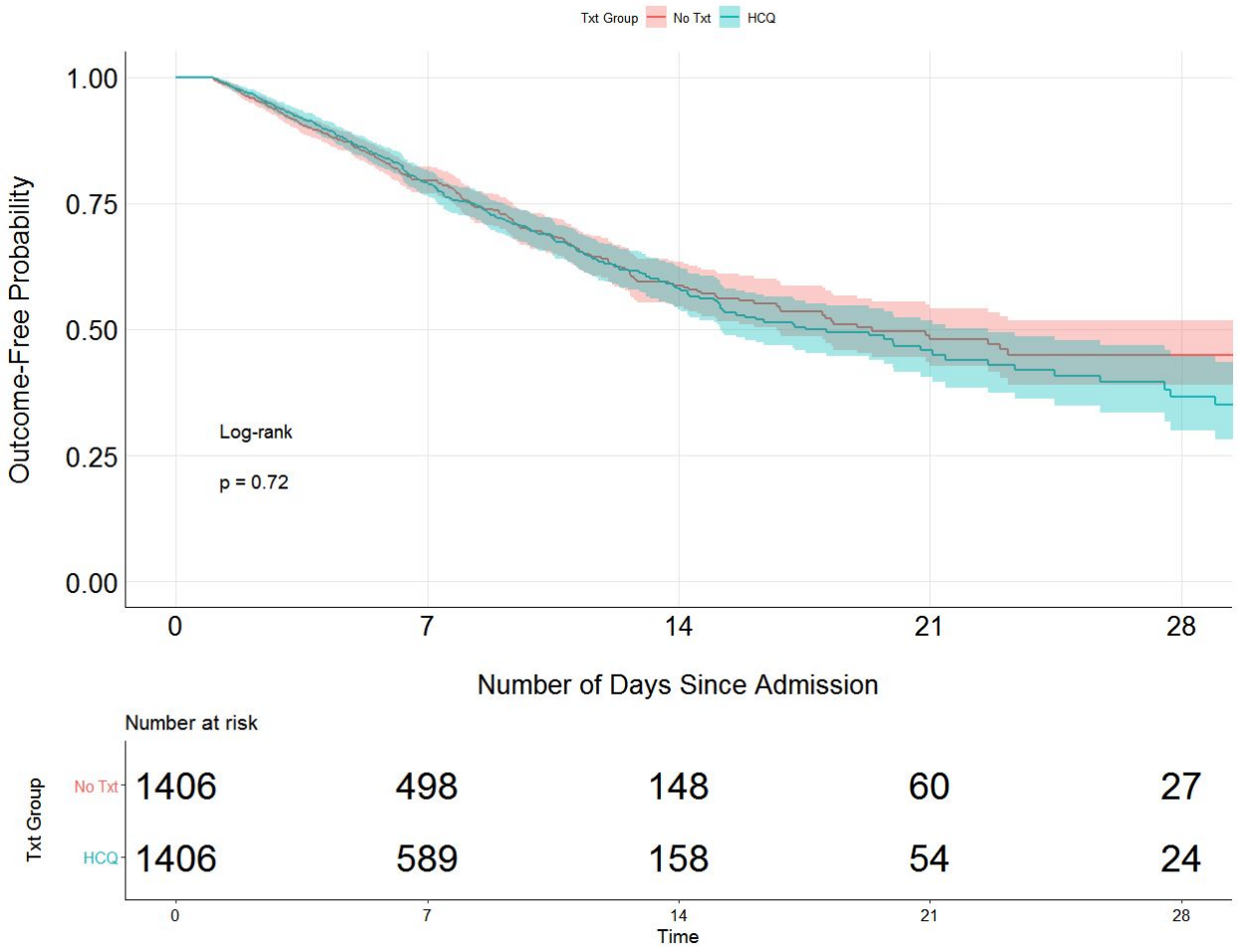


Figure 2. Kaplan-Meier curve showing freedom from composite end point of intubation or inpatient mortality by different time period

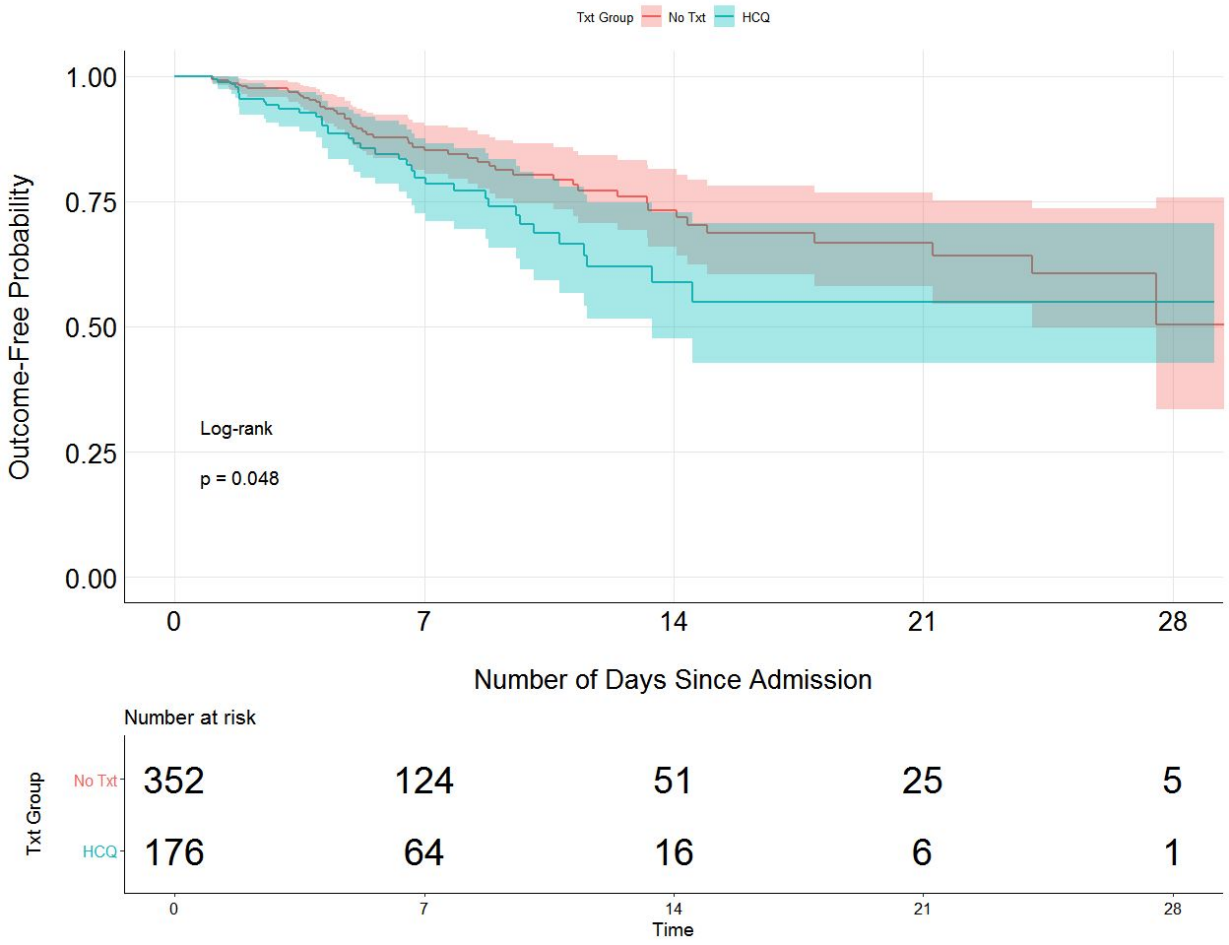
a. Pre-FDA approval



b. FDA approval



c. FDA warning



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Examination of patient characteristics and hydroxychloroquine use based on U.S. Food and Drug Administration's recommendation: a cross-sectional analysis in New York

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Title: **Examination of patient characteristics and hydroxychloroquine use based on U.S. Food and Drug Administration's recommendation: a cross-sectional analysis in New York**

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Abstract (300/300 words)

Objective: To describe the pattern of hydroxychloroquine use and examine the association between hydroxychloroquine use and clinical outcomes arising from changes in the U.S. Food and Drug Administration (FDA)'s recommendation during the COVID-19 pandemic.

Design: A retrospective cross-sectional analysis.

Setting and Participants: We included hospitalized adult patients at Northwell Health hospitals with confirmed COVID-19 infections between March 1, 2020 and May 11, 2020. We categorized changes in the FDA recommendation as pre-FDA approval (March 1-March 27, 2020), FDA approval (March 28-April 23, 2020), and FDA warning (April 24-May 11, 2020). The hydroxychloroquine treated group received at least one dose within 48 hours of hospital admission.

Primary outcome: A composite of intubation and inpatient death.

Results: The percentages of patients who were treated with hydroxychloroquine were 192/2202 (8.7%) pre-FDA approval, 2902/6741 (43.0%) FDA approval, and 176/1066 (16.5%) FDA warning period (p-value<0.001). Using propensity score-matching, there was a higher rate of the composite outcome among patients treated with hydroxychloroquine (49/192, 25.5%) compared to no hydroxychloroquine (66/384, 17.2%) in the pre-FDA approval period (p-value=0.03) but not in the FDA-approval period (25.5% vs 22.6%, p=0.08) or the FDA warning (21.0% vs 15.1%, p=0.11) periods. Coincidently, there was an increase in number of COVID-19 patients and disease severity during the FDA approval period (24.1% during FDA approval versus 21.4% during pre-FDA approval period). Hydroxychloroquine use was associated with increased odds of the composite outcome during the pre-FDA approval period (OR=1.65 [1.09-2.51]) but not

during the FDA approval (OR=1.17 [0.99-1.39]) and FDA warning (OR=1.50 [0.94-2.39]) periods.

Conclusions: Hydroxychloroquine use was associated with adverse clinical outcomes only during the pre-FDA approval period but not during the FDA-approval and warning periods, even after adjusting for concurrent changes in the percentage of COVID-19 patients treated with hydroxychloroquine and the number (and disease severity) of hospitalized patients with COVID-19 infections.

Strengths and limitations

- This study provides insights into how changes in FDA recommendations impact physicians' behaviors during a pandemic.
- The study utilizes data from a large integrated health system, which include a diverse population throughout New York City, Long Island, and Westchester County.
- This study uses propensity score-matching within each FDA recommendation, to ensure that patients admitted in the FDA approval period are not matched to patients in the pre-FDA approval or FDA warning period.
- Due to the observational study design, this study does not establish causal relationship between hydroxychloroquine treatment and outcomes.

Introduction

Coronavirus Disease 2019 (COVID-19), which causes severe acute respiratory syndrome, has spread globally. One consequence has been the unprecedented number of intensive care unit (ICU) admissions requiring mechanical ventilation in many countries. The mortality of patients on mechanical ventilation has been reported to be 60-80% with an overall hospital mortality of 20-25% during the beginning of the pandemic.[1,2] More recent studies have shown lower inpatient mortality, but COVID-19 still causes significant morbidity and mortality.[3,4] As of November 11, 2020, over 53 million people have been infected with COVID-19 and 1.3 million deaths have been reported globally.[5] Although multiple vaccines are in preparation or have begun clinical testing, data on safety and efficacy required to immunize the general public is currently unavailable and may be months to years away. Therefore, the need to identify medications that are associated with slowed COVID-19 progression or decreased mortality remains urgent.

During the early months of the COVID-19 pandemic, hydroxychloroquine, a medication commonly used to prevent malaria infection and treat autoimmune diseases, gained global attention for its effectiveness in treating COVID-19 *in vitro*.[6-11] Hydroxychloroquine is found to reduce the entry of coronavirus into a cell through interference with the terminal glycosylation of angiotensin-converting enzyme 2 receptor, which inhibits viral replication.[6,8] Additionally, hydroxychloroquine has immunomodulatory activity, and may inhibit cytokine production and prevent the occurrence of cytokine storm.[12] Early studies examining the treatment of COVID-19 with hydroxychloroquine showed mixed results, with some studies showing no average benefit in outcomes, including intubation or inpatient mortality, but other studies showing worse outcomes.[13-22] A recent randomized clinical trial study examining the effects of

hydroxychloroquine has found no difference in clinical outcomes between patients treated with and without hydroxychloroquine.[23]

However, no study has accounted for how changes in recommendations for hydroxychloroquine by the United States Food and Drug Administration (FDA) affected outcomes of patients treated for COVID-19. On March 28, 2020, the FDA issued an Emergency Use Authorization for hydroxychloroquine in the treatment of COVID-19 infection. During this time, there was also an increased number of hospitalized patients with COVID-19, which may have resulted in changes in hospital capacity and disease severity.[5] Subsequently, on April 24, 2020, the FDA cautioned against using hydroxychloroquine for COVID-19 infection.[24] These changes in the recommendation of hydroxychloroquine as a treatment for COVID-19 infection may have impacted whether patients were treated with hydroxychloroquine for COVID-19. These two events occurring concurrently could affect the association between hydroxychloroquine and COVID-19 outcomes. Therefore, using data from one of the largest healthcare systems in the United States, we described the pattern of hydroxychloroquine use over time according to the FDA's position and examined the association between hydroxychloroquine use and patients' clinical outcomes based on changes in FDA recommendation.

Methods

Setting

This is a cross-sectional analysis of data from Northwell Health, the largest academic healthcare system in New York. Northwell Health serves approximately 11 million patients throughout Long Island, New York City, and Westchester County and has 23 affiliated healthcare facilities, including 12 acute care hospitals. The Institutional Review Board for the

Feinstein Institutes for Medical Research at Northwell Health approved this case series as minimal-risk research using data collected for routine clinical practice and waived the requirement for informed consent.

Data Source

Data for this study was obtained from the enterprise's inpatient electronic health record (EHR; Sunrise Clinical Manager, Allscripts, Chicago, IL), which covers 12 of Northwell Health's hospitals.

Study Population

The study population included all adult patients (n=13,258), aged 18 years and older, hospitalized at one of Northwell Health's 12 acute care hospitals between March 1, 2020 and May 11, 2020 with a diagnosis of COVID-19 confirmed by a positive result on polymerase chain reaction testing of a nasopharyngeal sample. For patients with multiple COVID-19 tests, they were considered to have a confirmed COVID-19 infection if any of the repeated tests within the same hospitalization returned positive. We excluded patients who died or were intubated within one day of hospitalization because their clinical outcomes were likely predetermined by pre-hospitalization factors. We also excluded patients who were discharged within one day of admission. Patients who were admitted to the obstetrics service were excluded as all obstetrics patients were screened for COVID-19 on their admission. For patients with multiple hospitalizations for COVID-19, we used their first hospitalization with a confirmed diagnosis of COVID-19. We excluded 3,249 patients who did not meet the inclusion and exclusion criteria.

Exposure

Patients were identified as treated with hydroxychloroquine if they received at least one dose within 48 hours of admission. The control group for this analysis consisted of patients who were not treated with hydroxychloroquine within 48 hours of admission. Patients who did not initially receive hydroxychloroquine within 48 hours but received the medication later in their hospitalization were kept in the control group. We excluded COVID-19 patients who were treated with azithromycin or a combination of hydroxychloroquine and azithromycin. We also excluded patients who were intubated prior to getting their first dose of hydroxychloroquine within 48 hours of admission.

Outcomes

The primary outcome of interest was a composite outcome of time to intubation or time to inpatient death. Time until composite event was censored at time of discharge for patients who were discharged alive with no intubation during their hospitalization. The rationale for the combined primary outcome was twofold: 1) many patients who deteriorated clinically died without being intubated, often due to transition to palliative care; and 2) hospitalization stays for intubated COVID-19 patients have been very long, and many intubated COVID-19 patients at the time of the analyses may not ultimately survive. For a sensitivity analysis, we used death as the outcome. We tracked all patients who were not discharged or died until June 1, 2020.

Covariates

We collected data on patients' demographic characteristics and comorbidities. Demographic characteristics included age, sex, race/ethnicity, and health insurance (commercial,

Medicaid, Medicare, other, and no insurance). We used patient-reported race and ethnicity information and categorized patients into one of five racial/ethnic groups: White, Black, Asian, Other/Multiracial, and Unknown/Declined. We also identified a subgroup of patients who received immunomodulatory medications, including steroids (prednisone or methylprednisolone), sarilumab, tocilizumab, anakinra, or colchicine, and included this information as a covariate. We identified the presence of the following comorbidities by *International Statistical Classification of Disease and Related Health Problems, Tenth Revision (ICD-10)* coding: cancer, coronary artery disease, hypertension, asthma, chronic obstructive pulmonary disease, diabetes, chronic liver disease, chronic kidney disease, and end stage renal disease. We calculated the Charlson Comorbidity Index, which is an index that predicts the 10-year survival of patients with multiple comorbidities, as a measure of total comorbidity burden.[25] The only covariate with missing data was BMI, and we categorized the BMI group as not obese (BMI less than 30kg/m^2), obese (BMI greater than or equal to 30kg/m^2), and missing BMI.

We categorized changes in FDA recommendation for hydroxychloroquine, into three time periods: 1) pre-FDA approval (March 1-March 27, 2020); 2) FDA approval (March 28-April 23, 2020); and 3) FDA warning (April 24-May 11, 2020).

Statistical analysis

All analyses were performed using version 3.5.2 of the R Programming Language (R Project for Statistical Computing, R Foundation, Vienna, Austria). We first performed chi-square and 2-sample t-tests to compare patient characteristics treated with hydroxychloroquine to no hydroxychloroquine (control).

We used propensity-score matching methods, 1:2 for the pre-FDA approval and the FDA warning periods and 1:1 for the FDA approval period, using the smaller group as a reference, within each period and applied the nearest-neighbor method to create a matched control sample. The propensity-score matching was performed within each period so that patients admitted within the FDA approval period were not matched to patients in the pre-FDA approval or FDA warning periods, so as not to confound the effect of different FDA recommendations.

We then took the following approach to conduct the analysis. We first performed logistic regressions to compare the propensity score-matched hydroxychloroquine group to the control group. For a time-to-event analysis, we used the Kaplan-Meier survival estimate and log-rank test We examined the Kaplan-Meier survival curves for the treatment group compared to the control group, separated by the different FDA recommendation periods. If a patient was discharged alive without intubation, data was censored at the time of hospital discharge. Then, we used Cox proportional-hazard regression models to estimate the association between the propensity-matched treatment group to the control group with respect to end point free survival time. We used the Schoenfeld residuals to test the proportional hazard assumption in the Cox model.

Results

Characteristics of the cohort

From a cohort of 10,009 patients, 3,270 (32.7%) were treated with hydroxychloroquine, 2,640 (26.4%) with neither hydroxychloroquine nor azithromycin, 1,289 (12.9%) with azithromycin only, and 2,810 (28.1%) with the combination hydroxychloroquine and

azithromycin. There were differences in the number of patients treated with or without hydroxychloroquine and/or azithromycin by admission period (Figure 1).

We found significant differences in the use of hydroxychloroquine and patient characteristics based on changes to FDA recommendation. Number and percentages of patients treated with hydroxychloroquine were 192/2202 (8.7%) pre-FDA approval, 2902/6741 (43.0%) during FDA approval, and 176/1066 (16.5%) during the FDA warning period (p-value<0.001). There was a significant increase in number of patients during the FDA approval period (March 28-April 23). During the pre-FDA approval period, there were 2,202 patients admitted with COVID-19 infection, but in the following periods, the number of patients admitted with COVID-19 infections was 6,741 (FDA approval period) and 1,066 (FDA warning period). Throughout the study, and independent of FDA periods, there were differences in sociodemographic and clinical characteristics between the treatment group compared to the control group (Table 1). Higher percentage of patients who were younger (36.8% vs 32.5% were less than 60 years old), male (59.9% vs 53.4%), and had commercial insurance (31.0% vs 24.2%) were treated with hydroxychloroquine (p-values<0.001). Presence of comorbidity was associated with hydroxychloroquine use (all p-values<0.05), except for asthma and diabetes, and chronic kidney disease.

Hydroxychloroquine groups (13.4%) had higher rates of intubation compared to the control group (7.0%) (p-value<0.001). Inpatient mortality was 20.2% for hydroxychloroquine versus 18.3% for no hydroxychloroquine treatment (p-value=0.01). A significantly higher percentage of patients treated with hydroxychloroquine (23.4%) reached the composite outcome compared to the control group (20.4%) (p-value=0.007). A higher percentage of patients on

hydroxychloroquine (52.8%) were treated concurrently with immunomodulatory medications compared to the control group (24.7%) (p-value<0.001).

After propensity-score matching within each time period, sociodemographic characteristics and comorbidity were similar between hydroxychloroquine and no hydroxychloroquine group (Table 2). There were 576 patients in the pre-FDA approval period, 2812 patients in the FDA approval period, and 528 FDA warning period. There was a higher composite outcome among patients treated with hydroxychloroquine (25.5%) compared to no hydroxychloroquine (17.2%) during the pre-FDA approval period (p-value=0.03) but no difference in the number of composite outcomes between hydroxychloroquine and no hydroxychloroquine groups in the FDA-approval period (25.5%, vs 22.6% p=0.08) or the FDA warning period (21.0 vs 15.1% %, p=0.11) (Table 3). In the univariate analysis, hydroxychloroquine use was associated with increased odds of the composite outcome during the pre-FDA approval period (OR=1.65 [1.09-2.51]) but there was no association during the FDA approval (OR=1.17 [0.99-1.39]) as well as the FDA warning period (OR=1.50 [0.94-2.39]).

Time-to event analysis

Figure 2 shows the Kaplan-Meier curves of freedom from the composite end point of intubation and inpatient mortality during the pre-FDA approval period, the FDA approval period, or the FDA warning period. The cox proportional-hazard regression models showed hydroxychloroquine use was associated with the composite outcome of intubation and inpatient mortality during the pre-FDA approval (hazard ratio=1.70 [1.17-2.48]) and the FDA warning (hazard ratio=1.53 [1.00-2.34]) period but not during the FDA approval period (hazard

ratio=1.03 [0.88-1.20]) (Table 3). The proportional hazards assumption was met in the cox regression model.

Discussion

In our study, while there were changes in percentage of COVID-19 patients treated with hydroxychloroquine with FDA recommendations, there was also a fluctuation of the number of hospitalized patients with COVID-19 infections during the FDA approval period. Hydroxychloroquine treatment was associated with increased composite outcome of intubation or death during pre-FDA approval period but not during FDA approval or FDA warning period. The overall association of hydroxychloroquine treatment among COVID-19 patients in our cohort was similar to previous studies showing no association between the treatment and primary end point of intubation or death.[13,14]

Although not captured in our study, hospitals during the FDA approval period had to manage sudden increases in critically ill patients. As hospitals were reaching their maximum capacity, coordinated efforts were made to ensure that there were adequate ventilators for patients with pulmonary complications, goals of care discussions for patients with poor prognosis, and an increase in ambulatory management to ensure medical care for all patients.[26-28] Therefore, patients who were admitted during this period may have had more severe disease, including hypoxia, requiring ventilators. This hypothesis is also consistent with the higher proportions of patients experiencing the composite outcome during this period. There was also an increased use of immunomodulators, which were more often used for patients with more complications, including acute respiratory distress syndrome, acute kidney injury, thrombosis,

etc.[1,29,30] Therefore, regardless of whether they were being treated with hydroxychloroquine or not, patients admitted during the FDA approval period had overall worse outcomes compared to patients admitted during other periods. Because of such differences in patient disease severity and hospital settings, we used propensity-score matching of patients within each period so that the patients treated in the pre-FDA approval or FDA warning periods were not matched with patients treated in the FDA approval period.

The lack of efficacy of hydroxychloroquine could be attributed to the severity of disease among patients receiving medication. The hypothesized mechanism of action of hydroxychloroquine is that it prevents the virus from entering cells and blocks viral replication.[6-8] These patients were hospitalized because of a severe course of disease, and therefore it is likely that viral replication was already high when hydroxychloroquine was administered. This may be particularly true for patients who were hospitalized during the FDA approved period because hospitals had a high number of COVID-19 patients requiring inpatient care. Also, hydroxychloroquine may have been administered to more severely ill patients and subsequently was associated with higher risk of intubation and/or inpatient mortality. We addressed this by propensity-score matching patients treated with hydroxychloroquine to no hydroxychloroquine. Of note, higher doses of hydroxychloroquine have been associated with adverse intermediate outcomes, including QTc prolongation, in another study.[31]

This study has several limitations. Due to the observational study design, this study does not establish causal relationships between medication treatment and outcomes. Also, this study is limited to the inpatient setting, therefore the study findings are not generalizable to outpatient or community settings. Though we did attempt to adjust for covariates, it is possible that the severity of illness and precise timing of treatment also may have influenced the association of

these medications with the outcome. There might be a subset of patients who were taking hydroxychloroquine prescribed by their ambulatory providers prior to their hospitalization. It is possible that some patients in the no hydroxychloroquine group were taking the medications or already had completed their 5-day course prior to hospitalization. There was a subset of patients in the control group who were treated with hydroxychloroquine or azithromycin after 48 hours because of their disease progression. The changes in the FDA recommendations probably also caused some patients admitted during the pre-FDA approval period to be treated with hydroxychloroquine during their prolonged hospitalizations. This could result in bias toward the null, that is, erroneously concluding no difference between hydroxychloroquine and control (Type II error). The strength of this study, however, is the inclusion of a large, diverse population, including racial and ethnic minorities, extending the generalizability of our study.

Regardless of FDA's recommendation for the drug, we did not observe any beneficial association of hydroxychloroquine use throughout the study period. In addition to changes in the FDA recommendation, this study addresses changes in case mix due to changes in number of COVID-19 patients being hospitalized. This study further confirms that hydroxychloroquine does not alter the clinical course among patients with COVID-19 infections in the inpatient setting where patients have more severe diseases. Additionally, recent evidence suggests that hydroxychloroquine treatment does not alter clinical outcomes among patients with milder symptoms and is not effective as pharmacologic prophylaxis.[32,33] On June 15, 2020, the FDA revoked the Emergency Use Authorization for hydroxychloroquine in the treatment of COVID-19 infection and this will further decrease the number of COVID-19 patients being treated with hydroxychloroquine.[34] These study results should not be used as guidance on whether or not to treat COVID-19 patients with or without hydroxychloroquine due to its observational design.

Data Availability Statement

The data that support the findings of this study are available on request from COVID19@northwell.edu. The data are not publicly available due to restrictions as it could compromise the privacy of research participants.

Conflict of Interest Disclosures

The authors report no real or apparent conflicts of interest.

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Role of the Funder/Sponsor

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The views expressed in this paper are those of the authors and do not represent the views of the National Institutes of Health, the United States Department of Health and Human Services, or any other government entity.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Figures

Figure 1. Number of COVID-19 patients treated with different medications

Figure 2. Kaplan-Meier curve showing freedom from composite end point of intubation or inpatient mortality by different time period

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Table 1. Patient characteristics before propensity-score matching, number (percentage) for categorical variable and mean (standard deviation) for continuous variable

	All (n=10,009)	HCQ (n=3,270)	No HCQ (n=2,640)	P-value*
Sociodemographic characteristics				
Age at admission, mean (SD)	64.99 (16.35)	64.29 (15.58)	66.87 (17.73)	<0.001
Age group				<0.001
18-49	1747 (17.5)	558 (17.1)	434 (16.4)	
50-59	1863 (18.6)	645 (19.7)	425 (16.1)	
60-69	2277 (22.7)	816 (25.0)	530 (20.1)	
70-79	2046 (20.4)	671 (20.5)	518 (19.6)	
80+	2076 (20.7)	580 (17.7)	733 (27.8)	
Male	5847 (58.4)	1959 (59.9)	1411 (53.4)	<0.001
Race				<0.001
White	3923 (39.2)	1151 (35.2)	1182 (44.8)	
Black	2104 (21.0)	632 (19.3)	581 (22.0)	
Asian	849 (8.5)	327 (10.0)	236 (8.9)	
Other/Multiracial	2648 (26.5)	958 (29.3)	540 (20.5)	
Unknown	485 (4.8)	202 (6.2)	101 (3.8)	
Health insurance				<0.001
Commercial	2947 (29.4)	1013 (31.0)	638 (24.2)	
Medicaid	2041 (20.4)	712 (21.8)	488 (18.5)	
Medicare	4754 (47.5)	1431 (43.8)	1453 (55.0)	
Other	133 (1.3)	46 (1.4)	45 (1.7)	
No insurance	134 (1.3)	68 (2.1)	16 (0.6)	
Comorbidity				
Cancer	832 (8.3)	238 (7.3)	278 (10.5)	<0.001
Coronary artery disease	1339 (13.4)	399 (12.2)	429 (16.2)	<0.001
Hypertension	6073 (60.7)	1973 (60.3)	1673 (63.4)	0.02
Peripheral artery/vascular disease	282 (2.8)	81 (2.5)	100 (3.8)	0.005
Asthma	842 (8.4)	271 (8.3)	198 (7.5)	0.29
Chronic obstructive pulmonary disease	639 (6.4)	168 (5.1)	174 (6.6)	0.02
Diabetes	3624 (36.2)	1233 (37.7)	945 (35.8)	0.14
Chronic liver disease	298 (3.0)	74 (2.3)	110 (4.2)	<0.001
Chronic kidney disease	507 (5.1)	155 (4.7)	152 (5.8)	0.09
End stage renal disease	461 (4.6)	144 (4.4)	168 (6.4)	0.001
Charlson Comorbidity Index, mean SD	4.89 (3.58)	4.56 (3.38)	5.74 (3.77)	<0.001
Obesity				<0.001
Obese	2810 (28.1)	1001 (30.6)	570 (21.6)	
Not obese	4632 (46.3)	1483 (45.4)	1296 (49.1)	
Missing BMI	2567 (25.6)	786 (24.0)	774 (29.3)	
BMI, mean (SD)	29.23 (7.06)	29.66 (7.04)	28.13 (7.14)	<0.001

Clinical outcomes				
Admission week				<0.001
Pre-FDA approval	2202 (22.0)	192 (5.9)	496 (18.8)	
FDA approval	6741 (67.3)	2902 (88.7)	1406 (53.3)	
FDA warning	1066 (10.7)	176 (5.4)	738 (28.0)	
Length of stay, mean (SD)	9.51 (9.60)	9.56 (9.14)	8.80 (9.27)	0.001
Immunomodulator use	4183 (41.8)	1727 (52.8)	651 (24.7)	<0.001
ICU stay	1985 (19.8)	583 (17.8)	426 (16.1)	0.09
Mechanical ventilation	1314 (13.1)	437 (13.4)	186 (7.0)	<0.001
Inpatient mortality	1983 (19.8)	660 (20.2)	482 (18.3)	0.01
Composite Outcome	2413 (24.1)	764 (23.4)	538 (20.4)	0.007

* Comparing hydroxychloroquine group to no treatment group

Table 2. Patient characteristics after propensity-score matching, number (percentage) for categorical variable and mean (standard deviation) for continuous variable

	Pre-FDA approval				FDA approval				FDA warning			
	HCQ (n=192)	No HCQ (n=384)	P-value*	SMD	HCQ (n=1406)	No HCQ (n=1406)	P-value*	SMD	HCQ (n=176)	No HCQ (n=352)	P-value*	SMD
Sociodemographic characteristics												
Age at admission, mean (SD)	61.1 (15.8)	62.8 (17.2)	0.26	0.101	67.8 (15.8)	67.3 (17.6)	0.42	0.03	66.2 (16.2)	66.3 (17.6)	0.94	0.007
Male	109 (56.8)	218 (56.8)	1.00	<0.001	740 (52.6)	765 (54.4)	0.36	0.036	92 (52.3)	194 (55.1)	0.60	0.057
Race			0.68	0.134			1.00	0.013			0.99	0.05
White	91 (47.4)	180 (46.9)			610 (43.4)	612 (43.5)			65 (36.9)	136 (38.6)		
Black	35 (18.2)	86 (22.4)			306 (21.8)	302 (21.5)			37 (21.0)	69 (19.6)		
Asian	17 (8.9)	37 (9.6)			143 (10.2)	143 (10.2)			12 (6.8)	25 (7.1)		
Other/Multiracial	44 (22.9)	72 (18.8)			297 (21.1)	296 (21.1)			53 (30.1)	106 (30.1)		
Unknown	5 (2.6)	9 (2.3)			50 (3.6)	53 (3.8)			9 (5.1)	16 (4.5)		
Health insurance			0.02	0.257			0.90	0.039			1.00	0.036
Commercial	91 (47.4)	134 (34.9)			306 (21.8)	321 (22.8)			44 (25.0)	92 (26.1)		
Medicaid	30 (15.6)	72 (18.8)			246 (17.5)	249 (17.7)			31 17.6)	62 (17.6)		
Medicare	71 (37.0)	178 (46.4)			819 (58.3)	805 (57.3)			92 (52.3)	182 (51.7)		
Other	0 (0.0)	0 (0.0)			27 (1.9)	22 (1.6)			6 (3.4)	11 (3.1)		
No insurance	0 (0.0)	0 (0.0)			8 (0.6)	9 (0.6)			3 (1.7)	5 (1.4)		
Comorbidity												
Cancer	10 (5.2)	25 (6.5)	0.67	0.055	134 (9.5)	151 (10.7)	0.32	0.04	16 (9.1)	30 (8.5)	0.96	0.02
Coronary artery disease	23 (12.0)	56 (14.6)	0.47	0.077	218 (15.5)	222 (15.8)	0.88	0.008	27 (15.3)	53 (15.1)	1.00	0.008
Hypertension	109 (56.8)	237 (61.7)	0.29	0.101	915 (65.1)	884 (62.9)	0.24	0.046	107 (60.8)	205 (58.2)	0.64	0.052
Peripheral artery/vascular disease	7 (3.6)	13 (3.4)	1.00	0.014	48 (3.4)	42 (3.0)	0.59	0.024	6 (3.4)	6 (1.7)	0.35	0.108
Asthma	24 (12.5)	35 (9.1)	0.26	0.109	88 (6.3)	100 (7.1)	0.41	0.034	17 (9.7)	32 (9.1)	0.96	0.019
Chronic obstructive pulmonary disease	9 (4.7)	23 (6.0)	0.65	0.058	83 (5.9)	87 (6.2)	0.81	0.012	14 (8.0)	29 (8.2)	1.00	0.01
Diabetes	70 (36.5)	138 (35.9)	0.98	0.011	515 (36.6)	508 (36.1)	0.81	0.01	68 (38.6)	131 (37.2)	0.82	0.029
Chronic liver disease	7 (3.6)	15 (3.9)	1.00	0.014	47 (3.3)	56 (4.0)	0.42	0.034	7 (4.0)	19 (5.4)	0.62	0.067
Chronic kidney disease	11 (5.7)	25 (6.5)	0.86	0.033	84 (6.0)	80 (5.7)	0.81	0.012	8 (4.5)	17 (4.8)	1.00	0.013

End stage renal disease	12 (6.2)	27 (7.0)	0.86	0.031	99 (7.0)	101 (7.2)	0.94	0.006	4 (2.3)	8 (2.3)	1.00	<0.001
Charlson Comorbidity Index, mean SD	4.23 (3.19)	4.73 (3.32)	0.09	0.152	5.72 (3.75)	5.69 (3.73)	0.84	0.008	5.03 (3.23)	5.01 (3.42)	0.96	0.005
Obesity			0.08	0.198			0.84	0.022			0.96	0.027
Obese	76 (39.6)	116 (30.2)			289 (20.6)	292 (20.8)			50 (28.4)	98 (27.8)		
Not obese	69 (35.9)	160 (41.7)			678 (48.2)	663 (47.2)			84 (47.7)	166 (47.2)		
Missing BMI	47 (24.5)	108 (28.1)			439 (31.2)	451 (32.1)			42 (23.9)	88 (25.0)		
Clinical outcomes												
Length of stay, mean (SD)	10.88 (11.20)	10.48 (11.79)	0.70	0.035	9.29 (8.66)	7.75 (7.82)	<0.001	0.187	8.67 (7.55)	8.28 (7.40)	0.57	0.053
Mechanical ventilation	33 (17.2)	29 (7.6)	0.001	0.296	168 (11.9)	85 (6.0)	<0.001	0.207	26 (14.8)	25 (7.1)	0.008	0.248
Inpatient mortality	31 (16.1)	55 (14.3)	0.32	0.272	318 (22.6)	294 (20.9)	0.32	0.086	32 (18.2)	46 (13.1)	1.00	0.079
Composite Outcome	49 (25.5)	66 (17.2)	0.03	0.204	359 (25.5)	318 (22.6)	0.08	0.068	37 (21.0)	53 (15.1)	0.11	0.156

* Comparing hydroxychloroquine group to no treatment group
SMD=Standardized mean difference

Table 3. Association between hydroxychloroquine use and the composite end point in the crude analysis and propensity-score matched analysis

Analysis	Results	P-value*
Composite outcome among patients at risk, n (%)		
Before propensity score matching		
All periods		
Overall	2080/10009 (23.9)	-
Hydroxychloroquine	764/3270 (23.4)	0.007
No HCQ	538/2640 (20.4)	
After propensity score matching		
Pre-FDA approval		
Hydroxychloroquine	49/192 (25.5)	0.03
No HCQ	66/384 (17.2)	
FDA approval		
Hydroxychloroquine	359/1406 (25.5)	0.08
No HCQ	318/1406 (22.6)	
FDA warning		
Hydroxychloroquine	37/176 (21.0)	0.11
No HCQ	53/352 (15.1)	
Univariate analysis - odds ratio [95% confidence interval]*		
Pre-FDA approval (reference: no HCQ)	1.65 [1.09-2.51]	0.02
FDA approval (reference: no HCQ)	1.17 [0.99-1.39]	0.07
FDA warning (reference: no HCQ)	1.50 [0.94-2.39]	0.09
Propensity-score matched analyses-hazard ratio [95% confidence interval]*		
Pre-FDA approval (reference: no HCQ)	1.70 [1.17-2.48]	0.005
FDA approval (reference: no HCQ)	1.03 [0.88-1.20]	0.72
FDA warning (reference: no HCQ)	1.53 [1.00-2.34]	0.05

* Comparing hydroxychloroquine group to no treatment group

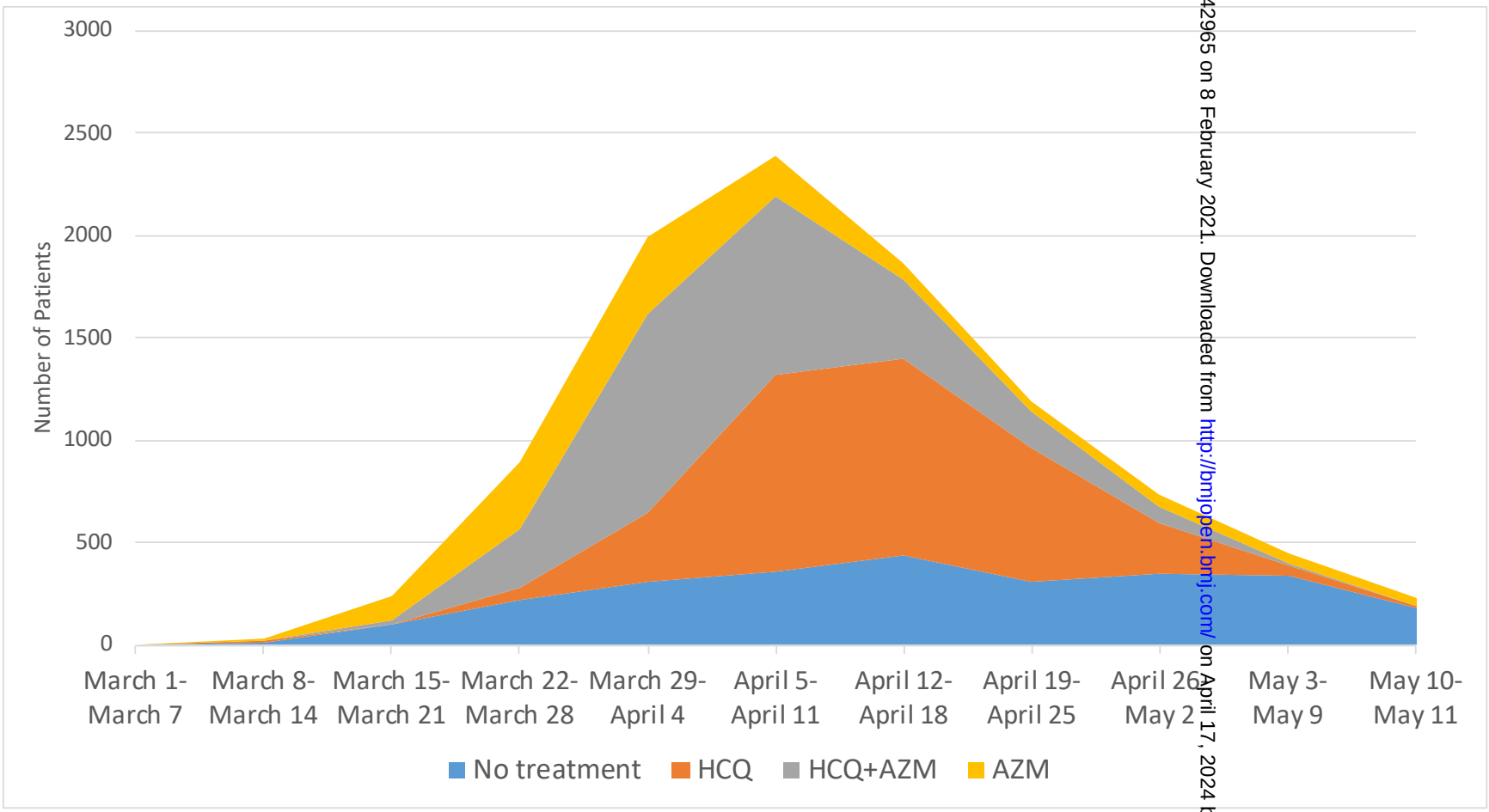
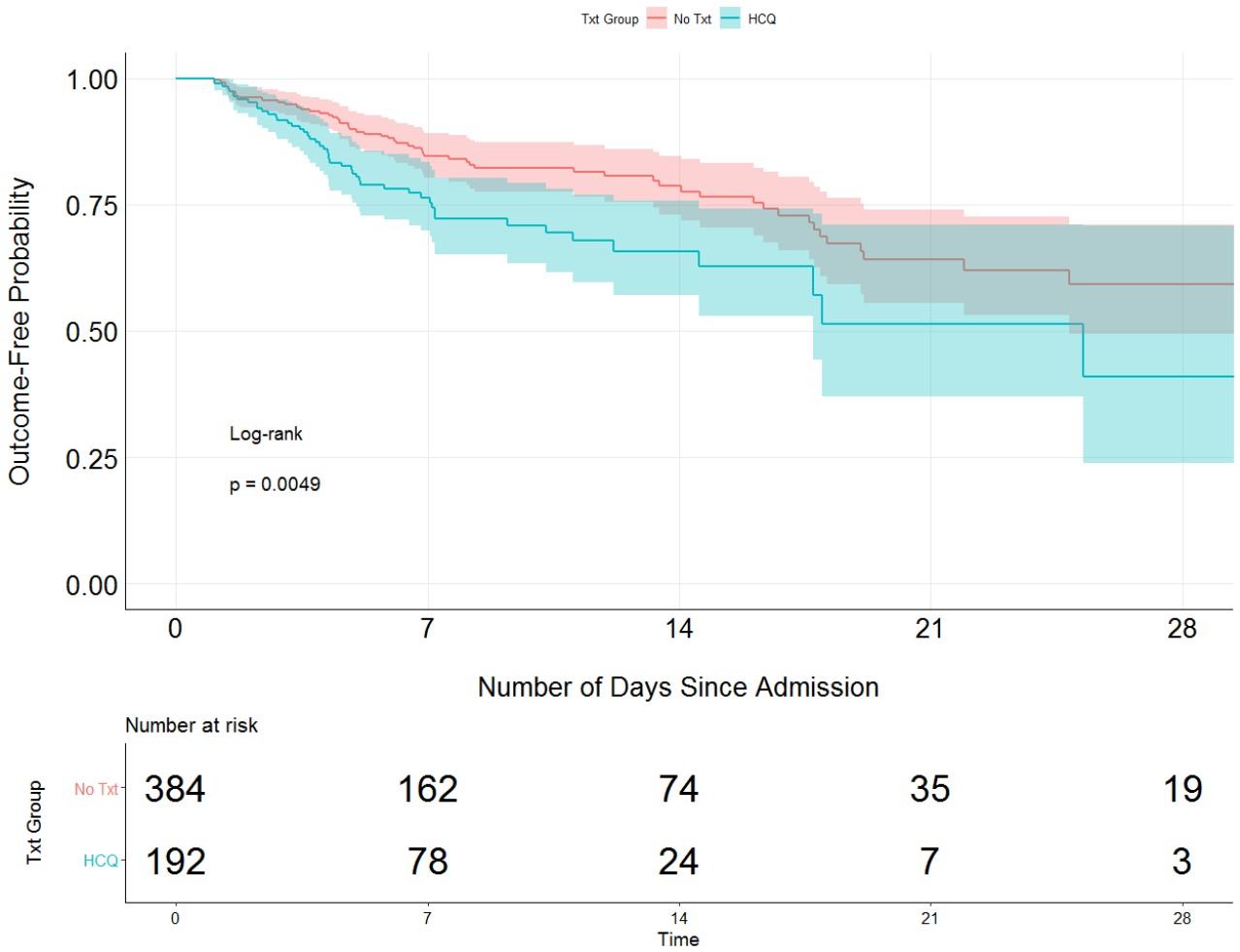
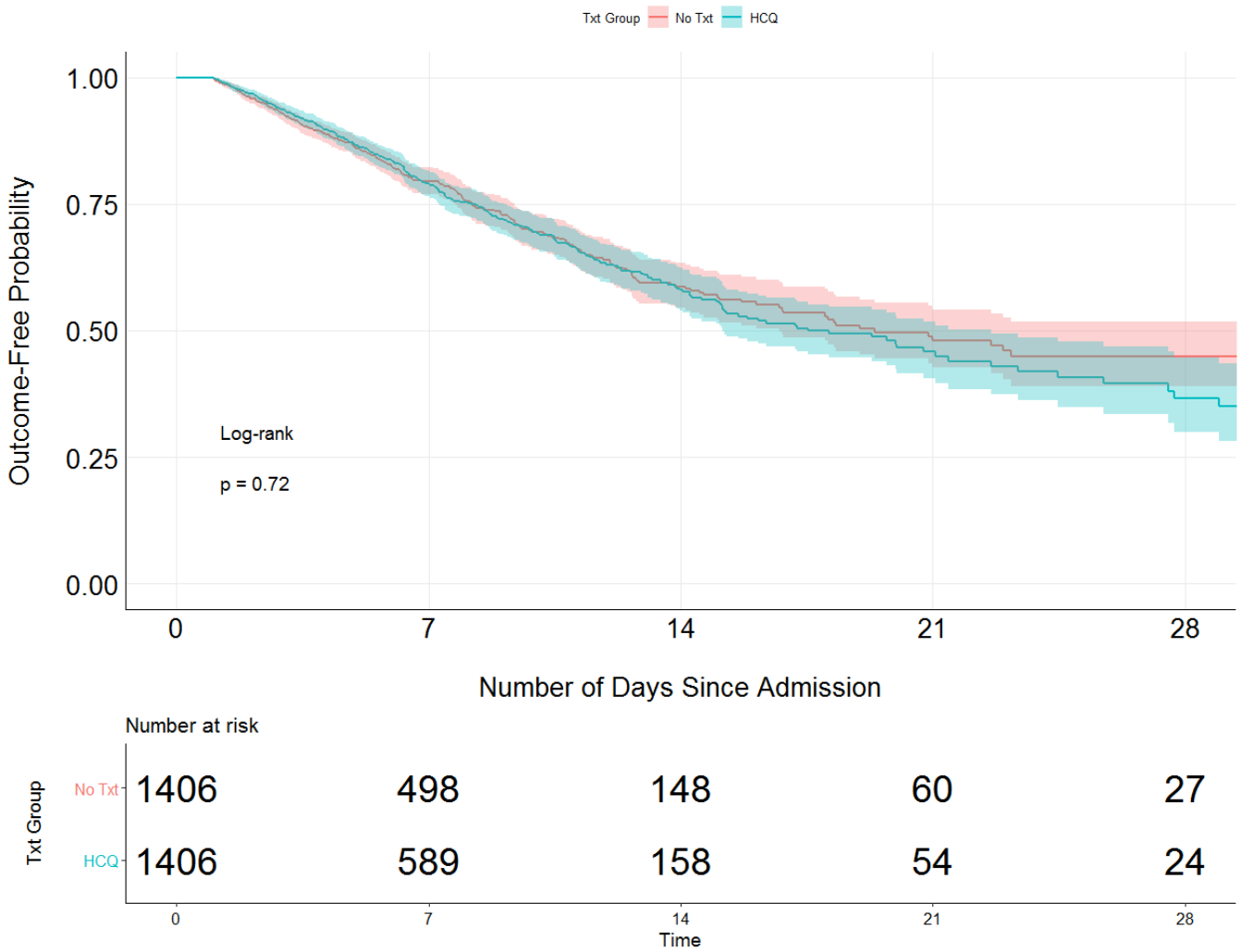


Figure 1. Trends in COVID-19 patients treated with different medications



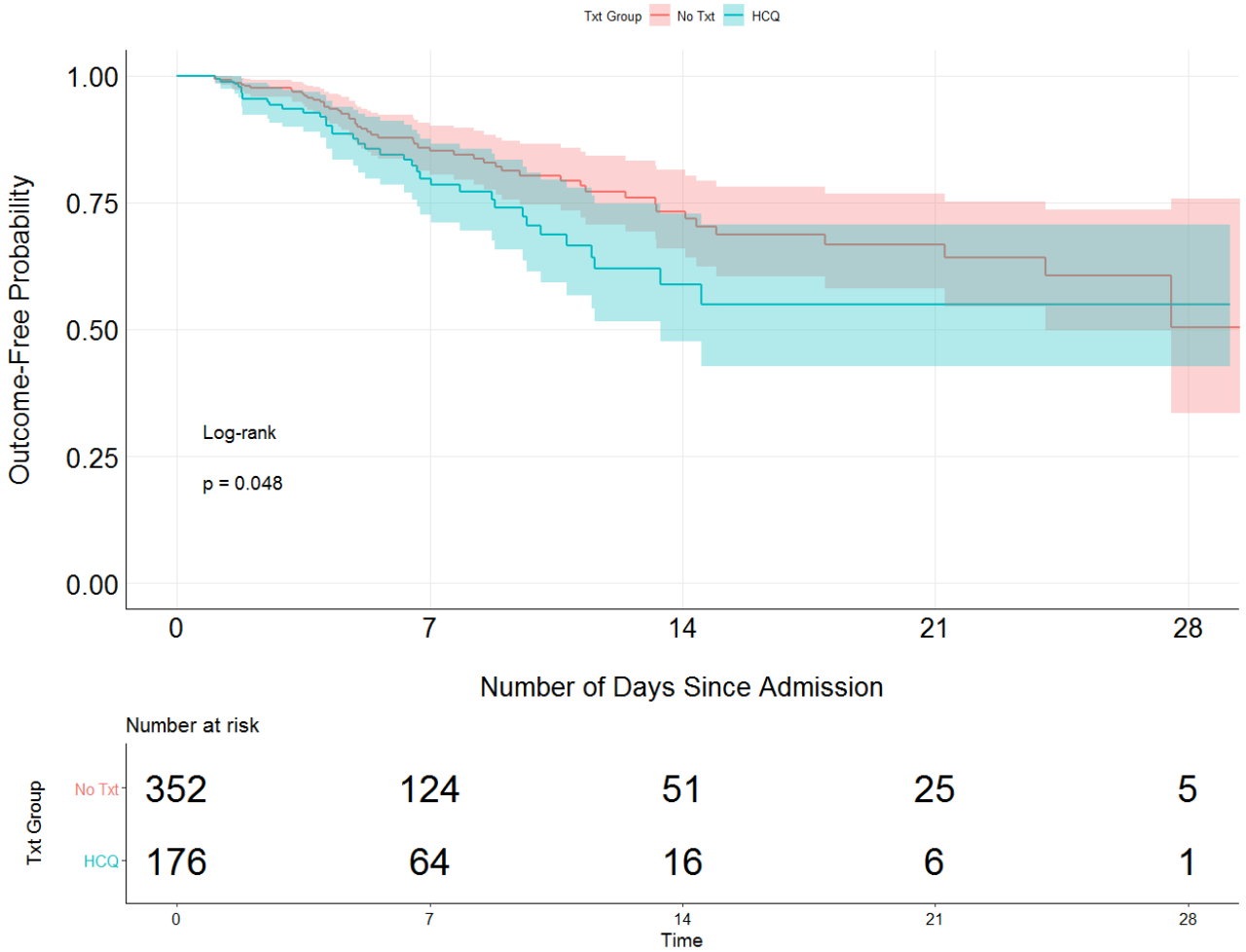
a. Pre-FDA approval

Figure 2. Kaplan-Meier curve showing freedom from composite end point of intubation or inpatient mortality by different time period



b. FDA approval

Figure 2. Kaplan-Meier curve showing freedom from composite end point of intubation or inpatient mortality by different time period



c. FDA warning

Figure 2. Kaplan-Meier curve showing freedom from composite end point of intubation or inpatient mortality by different time period

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 2 and 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 5 and 6
Objectives	3	State specific objectives, including any prespecified hypotheses Page 6 lines 13-16
Methods		
Study design	4	Present key elements of study design early in the paper Page 6 line 20
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 6 lines 19-Page 7 line 3, Page 7 lines 11-14, Page 8 lines 19
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants Page 7 lines 10-22
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 8 lines 4-Page 9 line 16
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 7 lines 5- 8
Bias	9	Describe any efforts to address potential sources of bias Page 10 lines 1-6
Study size	10	Explain how the study size was arrived at Page 7 lines 10-22
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page 8 line 21- Page 9 line 13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Page 9 line 18-Page 10 line 16
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed Page 9 lines 12-13
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses Page 8 lines 18-19
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 7 lines 11-15, line 22
		(b) Give reasons for non-participation at each stage

		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Page 10 line 20-page 12 line 14
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures Page 12 lines 6-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Page 12 lines 6-Page 13 line 2
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 13 lines 5-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 14 line 18-Page 15 line 9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 14 lines 6-17
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 15 lines 9-10
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 16 lines 9-12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Examination of patient characteristics and hydroxychloroquine use based on U.S. Food and Drug Administration's recommendation: a cross-sectional analysis in New York

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Title: **Examination of patient characteristics and hydroxychloroquine use based on U.S. Food and Drug Administration's recommendation: a cross-sectional analysis in New York**

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Critical revision of the manuscript for important intellectual content: all authors
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2,761 words
5 tables/figure

Abstract (300/300 words)

Objective: To describe the pattern of hydroxychloroquine use and examine the association between hydroxychloroquine use and clinical outcomes arising from changes in the U.S. Food and Drug Administration (FDA)'s recommendation during the COVID-19 pandemic.

Design: A retrospective cross-sectional analysis.

Setting and Participants: We included hospitalized adult patients at Northwell Health hospitals with confirmed COVID-19 infections between March 1, 2020 and May 11, 2020. We categorized changes in the FDA recommendation as pre-FDA approval (March 1-March 27, 2020), FDA approval (March 28-April 23, 2020), and FDA warning (April 24-May 11, 2020). The hydroxychloroquine treated group received at least one dose within 48 hours of hospital admission.

Primary outcome: A composite of intubation and inpatient death.

Results: The percentages of patients who were treated with hydroxychloroquine were 192/2202 (8.7%) pre-FDA approval, 2902/6741 (43.0%) FDA approval, and 176/1066 (16.5%) FDA warning period (p-value<0.001). Using propensity score-matching, there was a higher rate of the composite outcome among patients treated with hydroxychloroquine (49/192, 25.5%) compared to no hydroxychloroquine (66/384, 17.2%) in the pre-FDA approval period (p-value=0.03) but not in the FDA-approval period (25.5% vs 22.6%, p=0.08) or the FDA warning (21.0% vs 15.1%, p=0.11) periods. Coincidently, there was an increase in number of COVID-19 patients and disease severity during the FDA approval period (24.1% during FDA approval versus 21.4% during pre-FDA approval period). Hydroxychloroquine use was associated with increased odds of the composite outcome during the pre-FDA approval period (OR=1.65 [1.09-2.51]) but not

during the FDA approval (OR=1.17 [0.99-1.39]) and FDA warning (OR=1.50 [0.94-2.39]) periods.

Conclusions: Hydroxychloroquine use was associated with adverse clinical outcomes only during the pre-FDA approval period but not during the FDA-approval and warning periods, even after adjusting for concurrent changes in the percentage of COVID-19 patients treated with hydroxychloroquine and the number (and disease severity) of hospitalized patients with COVID-19 infections.

Strengths and limitations

- This study examines hydroxychloroquine use with changes in the FDA recommendations during a COVID-19 pandemic.
- The study utilizes data from a large integrated health system, which include a diverse population throughout New York City, Long Island, and Westchester County.
- This study uses propensity score-matching within each FDA recommendation, to ensure that patients admitted in the FDA approval period are not matched to patients in the pre-FDA approval or FDA warning period.
- Due to the observational study design, this study does not establish causal relationship between hydroxychloroquine treatment and COVID-19 clinical outcomes.

Introduction

Coronavirus Disease 2019 (COVID-19), which causes severe acute respiratory syndrome, has spread globally. One consequence has been the unprecedented number of intensive care unit (ICU) admissions requiring mechanical ventilation in many countries. The mortality of patients on mechanical ventilation has been reported to be 60-80% with an overall hospital mortality of 20-25% during the beginning of the pandemic.[1,2] More recent studies have shown lower inpatient mortality, but COVID-19 still causes significant morbidity and mortality.[3,4] As of November 11, 2020, over 53 million people have been infected with COVID-19 and 1.3 million deaths have been reported globally.[5] Although multiple vaccines are in preparation or have begun clinical testing, data on safety and efficacy required to immunize the general public is currently unavailable and may be months to years away. Therefore, the need to identify medications that are associated with slowed COVID-19 progression or decreased mortality remains urgent.

During the early months of the COVID-19 pandemic, hydroxychloroquine, a medication commonly used to prevent malaria infection and treat autoimmune diseases, gained global attention for its effectiveness in treating COVID-19 *in vitro*.[6-11] Hydroxychloroquine is found to reduce the entry of coronavirus into a cell through interference with the terminal glycosylation of angiotensin-converting enzyme 2 receptor, which inhibits viral replication.[6,8] Additionally, hydroxychloroquine has immunomodulatory activity, and may inhibit cytokine production and prevent the occurrence of cytokine storm.[12] Early studies examining the treatment of COVID-19 with hydroxychloroquine showed mixed results, with some studies showing no average benefit in outcomes, including intubation or inpatient mortality, but other studies showing worse outcomes.[13-22] A recent randomized clinical trial study examining the effects of

hydroxychloroquine has found no difference in clinical outcomes between patients treated with and without hydroxychloroquine.[23]

However, no study has accounted for how changes in recommendations for hydroxychloroquine by the United States Food and Drug Administration (FDA) affected outcomes of patients treated for COVID-19. On March 28, 2020, the FDA issued an Emergency Use Authorization for hydroxychloroquine in the treatment of COVID-19 infection. During this time, there was also an increased number of hospitalized patients with COVID-19, which may have resulted in changes in hospital capacity and disease severity.[5] Subsequently, on April 24, 2020, the FDA cautioned against using hydroxychloroquine for COVID-19 infection.[24] These changes in the recommendation of hydroxychloroquine as a treatment for COVID-19 infection may have impacted whether patients were treated with hydroxychloroquine for COVID-19. These two events occurring concurrently could affect the association between hydroxychloroquine and COVID-19 outcomes. Therefore, using data from one of the largest healthcare systems in the United States, we described the pattern of hydroxychloroquine use over time according to the FDA's position and examined the association between hydroxychloroquine use and patients' clinical outcomes based on changes in FDA recommendation.

Methods

Setting

This is a cross-sectional analysis of data from Northwell Health, the largest academic healthcare system in New York. Northwell Health serves approximately 11 million patients throughout Long Island, New York City, and Westchester County and has 23 affiliated healthcare facilities, including 12 acute care hospitals. The Institutional Review Board for the

Feinstein Institutes for Medical Research at Northwell Health approved this case series as minimal-risk research using data collected for routine clinical practice and waived the requirement for informed consent.

Data Source

Data for this study was obtained from the enterprise's inpatient electronic health record (EHR; Sunrise Clinical Manager, Allscripts, Chicago, IL), which covers 12 of Northwell Health's hospitals.

Study Population

The study population included all adult patients (n=13,258), aged 18 years and older, hospitalized at one of Northwell Health's 12 acute care hospitals between March 1, 2020 and May 11, 2020 with a diagnosis of COVID-19 confirmed by a positive result on polymerase chain reaction testing of a nasopharyngeal sample. For patients with multiple COVID-19 tests, they were considered to have a confirmed COVID-19 infection if any of the repeated tests within the same hospitalization returned positive. We excluded patients who died or were intubated within one day of hospitalization because their clinical outcomes were likely predetermined by pre-hospitalization factors. We also excluded patients who were discharged within one day of admission. Patients who were admitted to the obstetrics service were excluded as all obstetrics patients were screened for COVID-19 on their admission. For patients with multiple hospitalizations for COVID-19, we used their first hospitalization with a confirmed diagnosis of COVID-19. We excluded 3,249 patients who did not meet the inclusion and exclusion criteria.

Exposure

Patients were identified as treated with hydroxychloroquine if they received at least one dose within 48 hours of admission. The control group for this analysis consisted of patients who were not treated with hydroxychloroquine within 48 hours of admission. Patients who did not initially receive hydroxychloroquine within 48 hours but received the medication later in their hospitalization were kept in the control group. We excluded COVID-19 patients who were treated with azithromycin or a combination of hydroxychloroquine and azithromycin. We also excluded patients who were intubated prior to getting their first dose of hydroxychloroquine within 48 hours of admission.

Outcomes

The primary outcome of interest was a composite outcome of time to intubation or time to inpatient death. Time until composite event was censored at time of discharge for patients who were discharged alive with no intubation during their hospitalization. The rationale for the combined primary outcome was twofold: 1) many patients who deteriorated clinically died without being intubated, often due to transition to palliative care; and 2) hospitalization stays for intubated COVID-19 patients have been very long, and many intubated COVID-19 patients at the time of the analyses may not ultimately survive. For a sensitivity analysis, we used death as the outcome. We tracked all patients who were not discharged or died until June 1, 2020.

Covariates

We collected data on patients' demographic characteristics and comorbidities. Demographic characteristics included age, sex, race/ethnicity, and health insurance (commercial,

Medicaid, Medicare, other, and no insurance). We used patient-reported race and ethnicity information and categorized patients into one of five racial/ethnic groups: White, Black, Asian, Other/Multiracial, and Unknown/Declined. We also identified a subgroup of patients who received immunomodulatory medications, including steroids (prednisone or methylprednisolone), sarilumab, tocilizumab, anakinra, or colchicine, and included this information as a covariate. We identified the presence of the following comorbidities by *International Statistical Classification of Disease and Related Health Problems, Tenth Revision (ICD-10)* coding: cancer, coronary artery disease, hypertension, asthma, chronic obstructive pulmonary disease, diabetes, chronic liver disease, chronic kidney disease, and end stage renal disease. We calculated the Charlson Comorbidity Index, which is an index that predicts the 10-year survival of patients with multiple comorbidities, as a measure of total comorbidity burden.[25] The only covariate with missing data was BMI, and we categorized the BMI group as not obese (BMI less than 30kg/m^2), obese (BMI greater than or equal to 30kg/m^2), and missing BMI.

We categorized changes in FDA recommendation for hydroxychloroquine, into three time periods: 1) pre-FDA approval (March 1-March 27, 2020); 2) FDA approval (March 28-April 23, 2020); and 3) FDA warning (April 24-May 11, 2020).

Statistical analysis

All analyses were performed using version 3.5.2 of the R Programming Language (R Project for Statistical Computing, R Foundation, Vienna, Austria). We first performed chi-square and 2-sample t-tests to compare patient characteristics treated with hydroxychloroquine to no hydroxychloroquine (control).

We used propensity-score matching methods, 1:2 for the pre-FDA approval and the FDA warning periods and 1:1 for the FDA approval period, using the smaller group as a reference, within each period and applied the nearest-neighbor method to create a matched control sample. The propensity-score matching was performed within each period so that patients admitted within the FDA approval period were not matched to patients in the pre-FDA approval or FDA warning periods, so as not to confound the effect of different FDA recommendations.

We then took the following approach to conduct the analysis. We first performed logistic regressions to compare the propensity score-matched hydroxychloroquine group to the control group. For a time-to-event analysis, we used the Kaplan-Meier survival estimate and log-rank test We examined the Kaplan-Meier survival curves for the treatment group compared to the control group, separated by the different FDA recommendation periods. If a patient was discharged alive without intubation, data was censored at the time of hospital discharge. Then, we used Cox proportional-hazard regression models to estimate the association between the propensity-matched treatment group to the control group with respect to end point free survival time. We used the Schoenfeld residuals to test the proportional hazard assumption in the Cox model.

Results

Characteristics of the cohort

From a cohort of 10,009 patients, 3,270 (32.7%) were treated with hydroxychloroquine, 2,640 (26.4%) with neither hydroxychloroquine nor azithromycin, 1,289 (12.9%) with azithromycin only, and 2,810 (28.1%) with the combination hydroxychloroquine and

azithromycin. There were differences in the number of patients treated with or without hydroxychloroquine and/or azithromycin by admission period (Figure 1).

We found significant differences in the use of hydroxychloroquine and patient characteristics based on changes to FDA recommendation. Number and percentages of patients treated with hydroxychloroquine were 192/2202 (8.7%) pre-FDA approval, 2902/6741 (43.0%) during FDA approval, and 176/1066 (16.5%) during the FDA warning period (p-value<0.001). There was a significant increase in number of patients during the FDA approval period (March 28-April 23). During the pre-FDA approval period, there were 2,202 patients admitted with COVID-19 infection, but in the following periods, the number of patients admitted with COVID-19 infections was 6,741 (FDA approval period) and 1,066 (FDA warning period). Throughout the study, and independent of FDA periods, there were differences in sociodemographic and clinical characteristics between the treatment group compared to the control group (Table 1). Higher percentage of patients who were younger (36.8% vs 32.5% were less than 60 years old), male (59.9% vs 53.4%), and had commercial insurance (31.0% vs 24.2%) were treated with hydroxychloroquine (p-values<0.001). Presence of comorbidity was associated with hydroxychloroquine use (all p-values<0.05), except for asthma and diabetes, and chronic kidney disease.

Hydroxychloroquine groups (13.4%) had higher rates of intubation compared to the control group (7.0%) (p-value<0.001). Inpatient mortality was 20.2% for hydroxychloroquine versus 18.3% for no hydroxychloroquine treatment (p-value=0.01). A significantly higher percentage of patients treated with hydroxychloroquine (23.4%) reached the composite outcome compared to the control group (20.4%) (p-value=0.007). A higher percentage of patients on

hydroxychloroquine (52.8%) were treated concurrently with immunomodulatory medications compared to the control group (24.7%) (p-value<0.001).

After propensity-score matching within each time period, sociodemographic characteristics and comorbidity were similar between hydroxychloroquine and no hydroxychloroquine group (Table 2). There were 576 patients in the pre-FDA approval period, 2812 patients in the FDA approval period, and 528 FDA warning period. There was a higher composite outcome among patients treated with hydroxychloroquine (25.5%) compared to no hydroxychloroquine (17.2%) during the pre-FDA approval period (p-value=0.03) but no difference in the number of composite outcomes between hydroxychloroquine and no hydroxychloroquine groups in the FDA-approval period (25.5%, vs 22.6% p=0.08) or the FDA warning period (21.0 vs 15.1% %, p=0.11) (Table 3). In the univariate analysis, hydroxychloroquine use was associated with increased odds of the composite outcome during the pre-FDA approval period (OR=1.65 [1.09-2.51]) but there was no association during the FDA approval (OR=1.17 [0.99-1.39]) as well as the FDA warning period (OR=1.50 [0.94-2.39]).

Time-to event analysis

Figure 2 shows the Kaplan-Meier curves of freedom from the composite end point of intubation and inpatient mortality during the pre-FDA approval period, the FDA approval period, or the FDA warning period. The cox proportional-hazard regression models showed hydroxychloroquine use was associated with the composite outcome of intubation and inpatient mortality during the pre-FDA approval (hazard ratio=1.70 [1.17-2.48]) and the FDA warning (hazard ratio=1.53 [1.00-2.34]) period but not during the FDA approval period (hazard

ratio=1.03 [0.88-1.20]) (Table 3). The proportional hazards assumption was met in the cox regression model.

Discussion

In our study, while there were changes in percentage of COVID-19 patients treated with hydroxychloroquine with FDA recommendations, there was also a fluctuation of the number of hospitalized patients with COVID-19 infections during the FDA approval period. Hydroxychloroquine treatment was associated with increased composite outcome of intubation or death during pre-FDA approval period but not during FDA approval or FDA warning period. The overall association of hydroxychloroquine treatment among COVID-19 patients in our cohort was similar to previous studies showing no association between the treatment and primary end point of intubation or death.[13,14]

Although not captured in our study, hospitals during the FDA approval period had to manage sudden increases in critically ill patients. As hospitals were reaching their maximum capacity, coordinated efforts were made to ensure that there were adequate ventilators for patients with pulmonary complications, goals of care discussions for patients with poor prognosis, and an increase in ambulatory management to ensure medical care for all patients.[26-28] Therefore, patients who were admitted during this period may have had more severe disease, including hypoxia, requiring ventilators. This hypothesis is also consistent with the higher proportions of patients experiencing the composite outcome during this period. There was also an increased use of immunomodulators, which were more often used for patients with more complications, including acute respiratory distress syndrome, acute kidney injury, thrombosis,

etc.[1,29,30] Therefore, regardless of whether they were being treated with hydroxychloroquine or not, patients admitted during the FDA approval period had overall worse outcomes compared to patients admitted during other periods. Because of such differences in patient disease severity and hospital settings, we used propensity-score matching of patients within each period so that the patients treated in the pre-FDA approval or FDA warning periods were not matched with patients treated in the FDA approval period.

The lack of efficacy of hydroxychloroquine could be attributed to the severity of disease among patients receiving medication. The hypothesized mechanism of action of hydroxychloroquine is that it prevents the virus from entering cells and blocks viral replication.[6-8] These patients were hospitalized because of a severe course of disease, and therefore it is likely that viral replication was already high when hydroxychloroquine was administered. This may be particularly true for patients who were hospitalized during the FDA approved period because hospitals had a high number of COVID-19 patients requiring inpatient care. Also, hydroxychloroquine may have been administered to more severely ill patients and subsequently was associated with higher risk of intubation and/or inpatient mortality. We addressed this by propensity-score matching patients treated with hydroxychloroquine to no hydroxychloroquine. Of note, higher doses of hydroxychloroquine have been associated with adverse intermediate outcomes, including QTc prolongation, in another study.[31]

This study has several limitations. Due to the observational study design, this study does not establish causal relationships between medication treatment and outcomes. Also, this study is limited to the inpatient setting, therefore the study findings are not generalizable to outpatient or community settings. Though we did attempt to adjust for covariates, it is possible that the severity of illness and precise timing of treatment also may have influenced the association of

these medications with the outcome. There might be a subset of patients who were taking hydroxychloroquine prescribed by their ambulatory providers prior to their hospitalization. It is possible that some patients in the no hydroxychloroquine group were taking the medications or already had completed their 5-day course prior to hospitalization. There was a subset of patients in the control group who were treated with hydroxychloroquine or azithromycin after 48 hours because of their disease progression. The changes in the FDA recommendations probably also caused some patients admitted during the pre-FDA approval period to be treated with hydroxychloroquine during their prolonged hospitalizations. This could result in bias toward the null, that is, erroneously concluding no difference between hydroxychloroquine and control (Type II error). The strength of this study, however, is the inclusion of a large, diverse population, including racial and ethnic minorities, extending the generalizability of our study.

Regardless of FDA's recommendation for the drug, we did not observe any beneficial association of hydroxychloroquine use throughout the study period. In addition to changes in the FDA recommendation, this study addresses changes in case mix due to changes in number of COVID-19 patients being hospitalized. This study further confirms that hydroxychloroquine does not alter the clinical course among patients with COVID-19 infections in the inpatient setting where patients have more severe diseases. Additionally, recent evidence suggests that hydroxychloroquine treatment does not alter clinical outcomes among patients with milder symptoms and is not effective as pharmacologic prophylaxis.[32,33] On June 15, 2020, the FDA revoked the Emergency Use Authorization for hydroxychloroquine in the treatment of COVID-19 infection and this will further decrease the number of COVID-19 patients being treated with hydroxychloroquine.[34] These study results should not be used as guidance on whether or not to treat COVID-19 patients with or without hydroxychloroquine due to its observational design.

Data Availability Statement

The data that support the findings of this study are available on request from COVID19@northwell.edu. The data are not publicly available due to restrictions as it could compromise the privacy of research participants.

Conflict of Interest Disclosures

The authors report no real or apparent conflicts of interest.

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Role of the Funder/Sponsor

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The views expressed in this paper are those of the authors and do not represent the views of the National Institutes of Health, the United States Department of Health and Human Services, or any other government entity.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Figures

Figure 1. Number of COVID-19 patients treated with different medications

Figure 2. Kaplan-Meier curve showing freedom from composite end point of intubation or inpatient mortality by different time period

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Table 1. Patient characteristics before propensity-score matching, number (percentage) for categorical variable and mean (standard deviation) for continuous variable

	All (n=10,009)	HCQ (n=3,270)	No HCQ (n=2,640)	P-value*
Sociodemographic characteristics				
Age at admission, mean (SD)	64.99 (16.35)	64.29 (15.58)	66.87 (17.73)	<0.001
Age group				<0.001
18-49	1747 (17.5)	558 (17.1)	434 (16.4)	
50-59	1863 (18.6)	645 (19.7)	425 (16.1)	
60-69	2277 (22.7)	816 (25.0)	530 (20.1)	
70-79	2046 (20.4)	671 (20.5)	518 (19.6)	
80+	2076 (20.7)	580 (17.7)	733 (27.8)	
Male	5847 (58.4)	1959 (59.9)	1411 (53.4)	<0.001
Race				<0.001
White	3923 (39.2)	1151 (35.2)	1182 (44.8)	
Black	2104 (21.0)	632 (19.3)	581 (22.0)	
Asian	849 (8.5)	327 (10.0)	236 (8.9)	
Other/Multiracial	2648 (26.5)	958 (29.3)	540 (20.5)	
Unknown	485 (4.8)	202 (6.2)	101 (3.8)	
Health insurance				<0.001
Commercial	2947 (29.4)	1013 (31.0)	638 (24.2)	
Medicaid	2041 (20.4)	712 (21.8)	488 (18.5)	
Medicare	4754 (47.5)	1431 (43.8)	1453 (55.0)	
Other	133 (1.3)	46 (1.4)	45 (1.7)	
No insurance	134 (1.3)	68 (2.1)	16 (0.6)	
Comorbidity				
Cancer	832 (8.3)	238 (7.3)	278 (10.5)	<0.001
Coronary artery disease	1339 (13.4)	399 (12.2)	429 (16.2)	<0.001
Hypertension	6073 (60.7)	1973 (60.3)	1673 (63.4)	0.02
Peripheral artery/vascular disease	282 (2.8)	81 (2.5)	100 (3.8)	0.005
Asthma	842 (8.4)	271 (8.3)	198 (7.5)	0.29
Chronic obstructive pulmonary disease	639 (6.4)	168 (5.1)	174 (6.6)	0.02
Diabetes	3624 (36.2)	1233 (37.7)	945 (35.8)	0.14
Chronic liver disease	298 (3.0)	74 (2.3)	110 (4.2)	<0.001
Chronic kidney disease	507 (5.1)	155 (4.7)	152 (5.8)	0.09
End stage renal disease	461 (4.6)	144 (4.4)	168 (6.4)	0.001
Charlson Comorbidity Index, mean SD	4.89 (3.58)	4.56 (3.38)	5.74 (3.77)	<0.001
Obesity				<0.001
Obese	2810 (28.1)	1001 (30.6)	570 (21.6)	
Not obese	4632 (46.3)	1483 (45.4)	1296 (49.1)	
Missing BMI	2567 (25.6)	786 (24.0)	774 (29.3)	
BMI, mean (SD)	29.23 (7.06)	29.66 (7.04)	28.13 (7.14)	<0.001

Clinical outcomes				
Admission week				<0.001
Pre-FDA approval	2202 (22.0)	192 (5.9)	496 (18.8)	
FDA approval	6741 (67.3)	2902 (88.7)	1406 (53.3)	
FDA warning	1066 (10.7)	176 (5.4)	738 (28.0)	
Length of stay, mean (SD)	9.51 (9.60)	9.56 (9.14)	8.80 (9.27)	0.001
Immunomodulator use	4183 (41.8)	1727 (52.8)	651 (24.7)	<0.001
ICU stay	1985 (19.8)	583 (17.8)	426 (16.1)	0.09
Mechanical ventilation	1314 (13.1)	437 (13.4)	186 (7.0)	<0.001
Inpatient mortality	1983 (19.8)	660 (20.2)	482 (18.3)	0.01
Composite Outcome	2413 (24.1)	764 (23.4)	538 (20.4)	0.007

* Comparing hydroxychloroquine group to no treatment group

Table 2. Patient characteristics after propensity-score matching, number (percentage) for categorical variable and mean (standard deviation) for continuous variable

	Pre-FDA approval			FDA approval			FDA warning		
	HCQ (n=192)	No HCQ (n=384)	SMD	HCQ (n=1406)	No HCQ (n=1406)	SMD	HCQ (n=176)	No HCQ (n=352)	SMD
Sociodemographic characteristics									
Age at admission, mean (SD)	61.1 (15.8)	62.8 (17.2)	0.101	67.8 (15.8)	67.3 (17.6)	0.03	66.2 (16.2)	66.3 (17.6)	0.007
Male	109 (56.8)	218 (56.8)	<0.001	740 (52.6)	765 (54.4)	0.036	92 (52.3)	194 (55.1)	0.057
Race			0.134			0.013			0.05
White	91 (47.4)	180 (46.9)		610 (43.4)	612 (43.5)		65 (36.9)	136 (38.6)	
Black	35 (18.2)	86 (22.4)		306 (21.8)	302 (21.5)		37 (21.0)	69 (19.6)	
Asian	17 (8.9)	37 (9.6)		143 (10.2)	143 (10.2)		12 (6.8)	25 (7.1)	
Other/Multiracial	44 (22.9)	72 (18.8)		297 (21.1)	296 (21.1)		53 (30.1)	106 (30.1)	
Unknown	5 (2.6)	9 (2.3)		50 (3.6)	53 (3.8)		9 (5.1)	16 (4.5)	
Health insurance			0.257			0.039			0.036
Commercial	91 (47.4)	134 (34.9)		306 (21.8)	321 (22.8)		44 (25.0)	92 (26.1)	
Medicaid	30 (15.6)	72 (18.8)		246 (17.5)	249 (17.7)		31 (17.6)	62 (17.6)	
Medicare	71 (37.0)	178 (46.4)		819 (58.3)	805 (57.3)		92 (52.3)	182 (51.7)	
Other	0 (0.0)	0 (0.0)		27 (1.9)	22 (1.6)		6 (3.4)	11 (3.1)	
No insurance	0 (0.0)	0 (0.0)		8 (0.6)	9 (0.6)		3 (1.7)	5 (1.4)	
Comorbidity									
Cancer	10 (5.2)	25 (6.5)	0.055	134 (9.5)	151 (10.7)	0.04	16 (9.1)	30 (8.5)	0.02
Coronary artery disease	23 (12.0)	56 (14.6)	0.077	218 (15.5)	222 (15.8)	0.008	27 (15.3)	53 (15.1)	0.008
Hypertension	109 (56.8)	237 (61.7)	0.101	915 (65.1)	884 (62.9)	0.046	107 (60.8)	205 (58.2)	0.052
Peripheral artery/vascular disease	7 (3.6)	13 (3.4)	0.014	48 (3.4)	42 (3.0)	0.024	6 (3.4)	6 (1.7)	0.108
Asthma	24 (12.5)	35 (9.1)	0.109	88 (6.3)	100 (7.1)	0.034	17 (9.7)	32 (9.1)	0.019
Chronic obstructive pulmonary disease	9 (4.7)	23 (6.0)	0.058	83 (5.9)	87 (6.2)	0.012	14 (8.0)	29 (8.2)	0.01
Diabetes	70 (36.5)	138 (35.9)	0.011	515 (36.6)	508 (36.1)	0.01	68 (38.6)	131 (37.2)	0.029
Chronic liver disease	7 (3.6)	15 (3.9)	0.014	47 (3.3)	56 (4.0)	0.034	7 (4.0)	19 (5.4)	0.067
Chronic kidney disease	11 (5.7)	25 (6.5)	0.033	84 (6.0)	80 (5.7)	0.012	8 (4.5)	17 (4.8)	0.013

End stage renal disease	12 (6.2)	27 (7.0)	0.031	99 (7.0)	101 (7.2)	0.006	4 (2.3)	8 (2.3)	<0.001
Charlson Comorbidity Index, mean SD	4.23 (3.19)	4.73 (3.32)	0.152	5.72 (3.75)	5.69 (3.73)	0.008	5.05 (3.23)	5.01 (3.42)	0.005
Obesity			0.198			0.022			0.027
Obese	76 (39.6)	116 (30.2)		289 (20.6)	292 (20.8)		50 (28.4)	98 (27.8)	
Not obese	69 (35.9)	160 (41.7)		678 (48.2)	663 (47.2)		84 (47.7)	166 (47.2)	
Missing BMI	47 (24.5)	108 (28.1)		439 (31.2)	451 (32.1)		42 (23.9)	88 (25.0)	
Clinical outcomes									
Length of stay, mean (SD)	10.88 (11.20)	10.48 (11.79)	0.035	9.29 (8.66)	7.75 (7.82)	0.187	8.67 (7.55)	8.28 (7.40)	0.053
Mechanical ventilation	33 (17.2)	29 (7.6)	0.296	168 (11.9)	85 (6.0)	0.207	26 (14.8)	25 (7.1)	0.248
Inpatient mortality	31 (16.1)	55 (14.3)	0.272	318 (22.6)	294 (20.9)	0.086	32 (18.2)	46 (13.1)	0.079
Composite Outcome	49 (25.5)	66 (17.2)	0.204	359 (25.5)	318 (22.6)	0.068	37 (21.0)	53 (15.1)	0.156

* Comparing hydroxychloroquine group to no treatment group

SMD=Standardized mean difference

Table 3. Association between hydroxychloroquine use and the composite end point in the crude analysis and propensity-score matched analysis

Analysis	Results	P-value*
Composite outcome among patients at risk, n (%)		
Before propensity score matching		
All periods		
Overall	2080/10009 (23.9)	-
Hydroxychloroquine	764/3270 (23.4)	0.007
No HCQ	538/2640 (20.4)	
After propensity score matching		
Pre-FDA approval		
Hydroxychloroquine	49/192 (25.5)	0.03
No HCQ	66/384 (17.2)	
FDA approval		
Hydroxychloroquine	359/1406 (25.5)	0.08
No HCQ	318/1406 (22.6)	
FDA warning		
Hydroxychloroquine	37/176 (21.0)	0.11
No HCQ	53/352 (15.1)	
Univariate analysis - odds ratio [95% confidence interval]*		
Pre-FDA approval (reference: no HCQ)	1.65 [1.09-2.51]	0.02
FDA approval (reference: no HCQ)	1.17 [0.99-1.39]	0.07
FDA warning (reference: no HCQ)	1.50 [0.94-2.39]	0.09
Propensity-score matched analyses-hazard ratio [95% confidence interval]*		
Pre-FDA approval (reference: no HCQ)	1.70 [1.17-2.48]	0.005
FDA approval (reference: no HCQ)	1.03 [0.88-1.20]	0.72
FDA warning (reference: no HCQ)	1.53 [1.00-2.34]	0.05

* Comparing hydroxychloroquine group to no treatment group

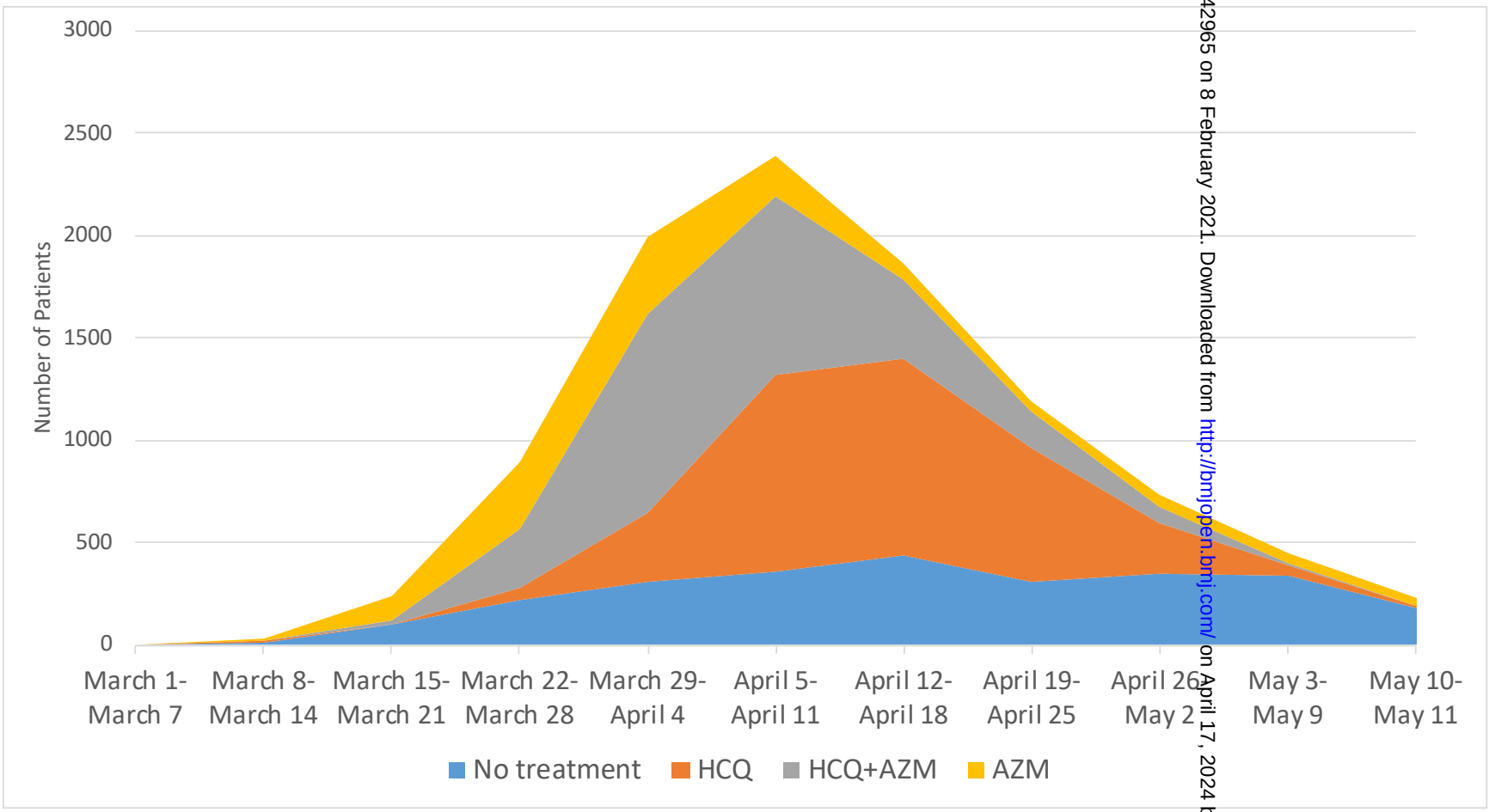
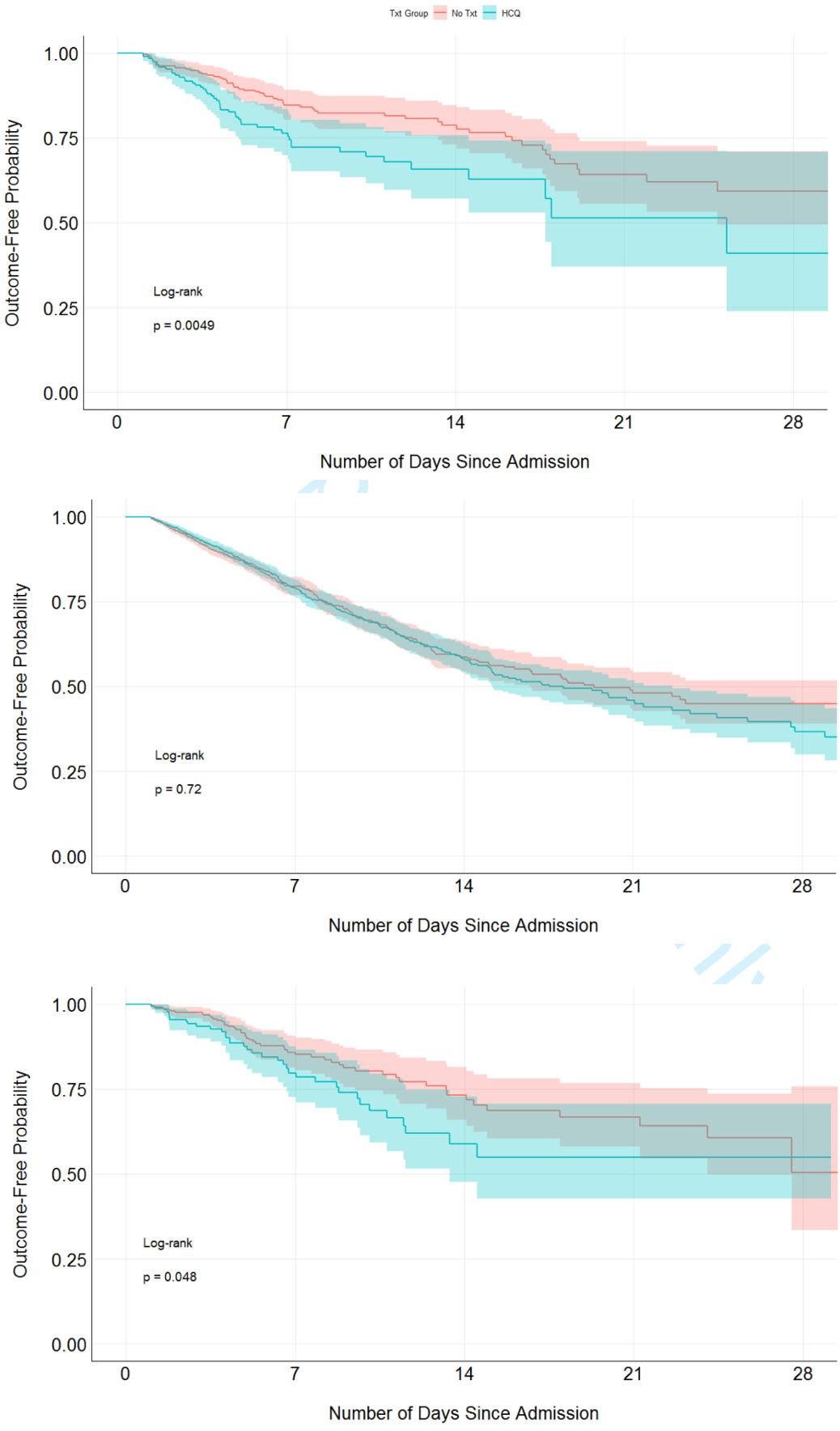


Figure 1. Trends in COVID-19 patients treated with different medications

Figure 2. Kaplan-Meier curve showing freedom from composite end point of intubation or inpatient mortality by different time period



STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 2 and 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 5 and 6
Objectives	3	State specific objectives, including any prespecified hypotheses Page 6 lines 13-16
Methods		
Study design	4	Present key elements of study design early in the paper Page 6 line 20
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 6 lines 19-Page 7 line 3, Page 7 lines 11-14, Page 8 lines 19
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants Page 7 lines 10-22
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 8 lines 4-Page 9 line 16
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 7 lines 5- 8
Bias	9	Describe any efforts to address potential sources of bias Page 10 lines 1-6
Study size	10	Explain how the study size was arrived at Page 7 lines 10-22
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page 8 line 21- Page 9 line 13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Page 9 line 18-Page 10 line 16
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed Page 9 lines 12-13
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses Page 8 lines 18-19
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 7 lines 11-15, line 22
		(b) Give reasons for non-participation at each stage

		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Page 10 line 20-page 12 line 14
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures Page 12 lines 6-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Page 12 lines 6-Page 13 line 2
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 13 lines 5-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 14 line 18-Page 15 line 9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 14 lines 6-17
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 15 lines 9-10
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 16 lines 9-12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.