ORIGINAL ARTICLE

Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19

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ABSTRACT

BACKGROUND

Hydroxychloroquine has been widely administered to patients with Covid-19 without robust evidence supporting its use.

METHODS

We examined the association between hydroxychloroquine use and intubation or death at a large medical center in New York City. Data were obtained regarding consecutive patients hospitalized with Covid-19, excluding those who were intubated, died, or discharged within 24 hours after presentation to the emergency department (study baseline). The primary end point was a composite of intubation or death in a time-to-event analysis. We compared outcomes in patients who received hydroxychloroquine with those in patients who did not, using a multivariable Cox model with inverse probability weighting according to the propensity score.

RESULTS

Of 1446 consecutive patients, 70 patients were intubated, died, or discharged within 24 hours after presentation and were excluded from the analysis. Of the remaining 1376 patients, during a median follow-up of 22.5 days, 811 (58.9%) received hydroxychloroquine (600 mg twice on day 1, then 400 mg daily for a median of 5 days); 45.8% of the patients were treated within 24 hours after presentation to the emergency department, and 85.9% within 48 hours. Hydroxychloroquine-treated patients were more severely ill at baseline than those who did not receive hydroxychloroquine (median ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen, 223 vs. 360). Overall, 346 patients (25.1%) had a primary end-point event (180 patients were intubated, of whom 66 subsequently died, and 166 died without intubation). In the main analysis, there was no significant association between hydroxychloroquine use and intubation or death (hazard ratio, 1.04, 95% confidence interval, 0.82 to 1.32). Results were similar in multiple sensitivity analyses.

CONCLUSIONS

In this observational study involving patients with Covid-19 who had been admitted to the hospital, hydroxychloroquine administration was not associated with either a greatly lowered or an increased risk of the composite end point of intubation or death. Randomized, controlled trials of hydroxychloroquine in patients with Covid-19 are needed. (Funded by the National Institutes of Health.)

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The aminoquinolines chloroquine and hydroxychloroquine are widely used in the treatment of malaria and rheumatic diseases, and they have been suggested as effective treatments for coronavirus disease 2019 (Covid-19) on the grounds of both antiinflammatory and antiviral effects.[1-4] In the United States, the Food and Drug Administration issued an Emergency Use Authorization on March 30, 2020, that allowed the use of these drugs in patients with Covid-19 who were not enrolled in clinical trials. Guidelines suggested that these drugs be administered to hospitalized patients who had evidence of pneumonia,[5] and to date, they have been used in many thousands of patients with acute Covid-19 around the world. However, to date, there have been no robust clinical trials that have shown efficacy of these agents for this illness, and the data that are available come from small studies that have either been uncontrolled or underpowered to detect meaningful clinical effects.

The original report of hydroxychloroquine as a treatment for Covid-19 described 26 patients who had been treated in an open-label, single-group study that involved contemporaneous, but nonrandomized controls in hospitals in France.[6] Patients were treated with hydroxychloroquine at a dose of 200 mg three times daily for 10 days. Data from this study were reported as showing the effectiveness of hydroxychloroquine in reducing the viral burden in treated patients (65.0% clearance by day 5, vs. 18.8% clearance by day 5 in untreated patients). However, data from 6 patients who received hydroxychloroquine were excluded from the analysis because of clinical worsening or loss to follow-up, which makes it difficult to interpret the findings.

Recent work suggests that hydroxychloroquine has more potent antiviral properties than chloroquine, as well as a better safety profile.[7] In accordance with clinical guidelines developed at our medical center, hydroxychloroquine was suggested as treatment for hospitalized patients with Covid-19 and respiratory difficulty, as indicated by a low resting oxygen saturation, during the period in which patients in this report were admitted.

We examined the association between hydroxychloroquine use and respiratory failure at a large medical center providing care to a substantial number of patients with Covid-19 in New York City. We hypothesized that hydroxychloroquine use would be associated with a lower risk of a composite end point of intubation or death in analyses that were adjusted for major predictors of respiratory failure and weighted according to propensity scores assessing the probability of hydroxychloroquine use.

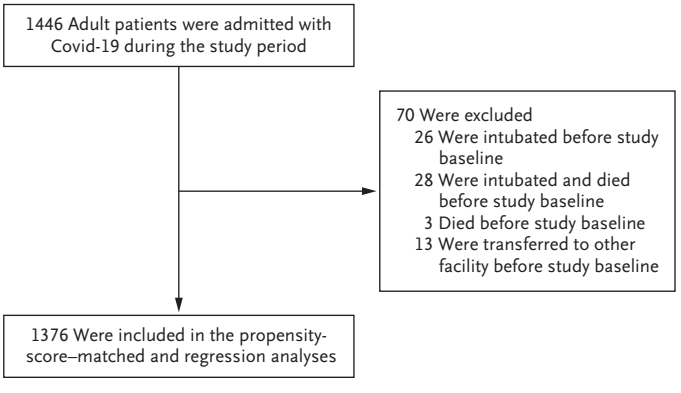

Figure 1. Study Cohort.
Study baseline was defined as 24 hours after arrival at the emergency department. Covid-19 denotes coronavirus disease 2019.

METHODS

SETTING

We conducted this study at New York–Presbyterian Hospital (NYP)–Columbia University Irving Medical Center (CUIMC), a quaternary, acute care hospital in northern Manhattan. We obtained samples from all admitted adults who had a positive test result for the virus SARS-CoV-2 from analysis of nasopharyngeal or oropharyngeal swab specimens obtained at any point during their hospitalization from March 7 to April 8, 2020. Follow-up continued through April 25, 2020. These tests were conducted by the New York State Department of Health until the NYP–CUIMC laboratory developed internal testing capability with a reverse-transcriptase–polymerase-chain-reaction assay on March 11, 2020. Patients who were intubated, who died, or who were transferred to another facility within 24 hours after presentation to the emergency department were excluded from the analysis. The institutional review board at CUIMC approved this analysis under an expedited review.

A guidance developed by the Department of Medicine and distributed to all the house staff and attending staff at our medical center suggested hydroxychloroquine as a therapeutic option for

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patients with Covid-19 who presented with moderate-to-severe respiratory illness, which was defined as a resting oxygen saturation of less than 94% while they were breathing ambient air. The suggested hydroxychloroquine regimen was a loading dose of 600 mg twice on day 1, followed by 400 mg daily for 4 additional days. Azithromycin at a dose of 500 mg on day 1 and then 250 mg daily for 4 more days in combination with hydroxychloroquine was an additional suggested therapeutic option. The azithromycin suggestion was removed on April 12, 2020, and the hydroxychloroquine suggestion was removed on April 29, 2020. The decision to prescribe either or both medications was left to the discretion of the treating team for each individual patient.

Patients receiving sarilumab were allowed to continue hydroxychloroquine. Patients receiving remdesivir as part of a randomized trial either did not receive or had completed a course of treatment with hydroxychloroquine.

DATA SOURCES

We obtained data from the NYP–CUIMC clinical data warehouse. This warehouse contains all the clinical data available on all inpatient and outpatient visits to one of the CUIMC facilities (see the Data Extraction section in the Supplementary Appendix, available with the full text of this article at NEJM.org). No data were manually abstracted from the electronic medical record or charts. The data obtained included patients' demographic details, insurance status, vital signs, laboratory test results, medication administration data, historical and current medication lists, historical and current diagnoses, clinical notes, historical discharge disposition for previous inpatient hospitalizations, and ventilator use data.

VARIABLES ASSESSED

From the clinical data warehouse, we obtained the following data elements for each patient: age; sex; patient-reported race and ethnic group; current insurance carrier; the first recorded vital signs on presentation; the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao_2:Fio_2) at admission, estimated with the use of methods developed by Brown and colleagues[8,9] (see the Data Extraction section in the Supplementary Appendix); the first recorded body-mass index as calculated for measured height and weight (the body-mass index is the weight in kilograms divided by the square of the height in meters), grouped on the basis of the Centers for Disease Control and Prevention guidelines for adults; the first recorded inpatient laboratory tests; past and current diagnoses; patient-reported smoking status; and medication administration at baseline. Details of the variables assessed are provided in the Supplementary Appendix.

HYDROXYCHLOROQUINE EXPOSURE

Patients were defined as receiving hydroxychloroquine if they were receiving it at study baseline or received it during the follow-up period before intubation or death. Study baseline was defined as 24 hours after arrival at the emergency department.

END POINT

The primary end point was the time from study baseline to intubation or death. For patients who died after intubation, the timing of the primary end point was defined as the time of intubation.

STATISTICAL ANALYSIS

We calculated bivariate frequencies to examine the associations among the preadmission variables described above. Patients without a primary end-point event had their data censored on April 25, 2020.

Cox proportional-hazards regression models were used to estimate the association between hydroxychloroquine use and the composite end point of intubation or death. An initial multivariable Cox regression model included demographic factors, clinical factors, laboratory tests, and medications. In addition, to help account for the nonrandomized treatment administration of hydroxychloroquine, we used propensity-score methods to reduce the effects of confounding. The individual propensities for receipt of hydroxychloroquine treatment were estimated with the use of a multivariable logistic-regression model that included the same covariates as the Cox regression model. Associations between hydroxychloroquine use and respiratory failure were then estimated by multivariable Cox regression models with the use of three propensity-score methods.

The primary analysis used inverse probability weighting. In the inverse-probability-weighted analysis, the predicted probabilities from the propensity-score model were used to calculate the stabilized inverse-probability-weighting weight.[10]

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Table 1. Characteristics of Patients Receiving or Not Receiving Hydroxychloroquine, before and after Propensity-Score Matching.*

Characteristic	Unmatched Patients		Propensity-Score–Matched Patients†	
	Hydroxychloroquine (N=811)	No Hydroxychloroquine (N=565)	Hydroxychloroquine (N=811)	No Hydroxychloroquine (N=274)
Age — no. (%)				
<40 yr	80 (9.9)	105 (18.6)	80 (9.9)	28 (10.2)
40–59 yr	217 (26.8)	142 (25.1)	217 (26.8)	69 (25.2)
60–79 yr	367 (45.3)	220 (38.9)	367 (45.3)	118 (43.1)
≥80 yr	147 (18.1)	98 (17.3)	147 (18.1)	59 (21.5)
Female sex — no. (%)	337 (41.6)	258 (45.7)	337 (41.6)	113 (41.2)
Race and ethnic group — no. (%)‡				
Non-Hispanic white	74 (9.1)	57 (10.1)	97 (12.0)	36 (13.1)
Non-Hispanic black	89 (11.0)	92 (16.3)	120 (14.8)	40 (14.6)
Hispanic	412 (50.8)	286 (50.6)	530 (65.4)	172 (62.8)
Other	48 (5.9)	36 (6.4)	64 (7.9)	26 (9.5)
Missing data	188 (23.2)	94 (16.6)	0	0
Body-mass index — no. (%)§				
<18.5	13 (1.6)	13 (2.3)	18 (2.2)	7 (2.6)
18.5–24.9	147 (18.1)	98 (17.3)	184 (22.7)	53 (19.3)
25.0–29.9	224 (27.6)	157 (27.8)	279 (34.4)	96 (35.0)
30.0–39.9	218 (26.9)	133 (23.5)	268 (33.0)	99 (36.1)
≥40.0	52 (6.4)	20 (3.5)	62 (7.6)	19 (6.9)
Missing data	157 (19.4)	144 (25.5)	0	0
Insurance — no. (%)				
Medicaid	165 (20.3)	146 (25.8)	166 (20.5)	54 (19.7)
Medicare	396 (48.8)	261 (46.2)	399 (49.2)	141 (51.5)
No insurance	79 (9.7)	49 (8.7)	79 (9.7)	29 (10.6)
Commercial insurance	166 (20.5)	106 (18.8)	167 (20.6)	50 (18.2)
Missing data	5 (0.6)	3 (0.5)	0	0
Current smoking — no. (%)	89 (11.0)	68 (12.0)	89 (11.0)	32 (11.7)
Past diagnoses — no. (%)				
Chronic lung disease¶	146 (18.0)	105 (18.6)	146 (18.0)	49 (17.9)
Diabetes	301 (37.1)	190 (33.6)	301 (37.1)	94 (34.3)
Hypertension	398 (49.1)	38 (6.7)	398 (49.1)	146 (53.3)
Cancer	109 (13.4)	67 (11.9)	109 (13.4)	35 (12.8)
Chronic kidney disease	133 (16.4)	105 (18.6)	133 (16.4)	61 (22.3)
Transplantation, HIV infection, or immune-suppressive medications	40 (4.9)	18 (3.2)	40 (4.9)	11 (4.0)
Medications at baseline — no. (%)				
Statin	308 (38)	197 (34.9)	308 (38)	107 (39.1)
ACE inhibitor or ARB	236 (29.1)	142 (25.1)	236 (29.1)	85 (31.0)
Systemic glucocorticoid	216 (26.6)	57 (10.1)	216 (26.6)	42 (15.3)
Direct oral anticoagulant or warfarin	76 (9.4)	47 (8.3)	76 (9.4)	24 (8.8)

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Table 1. (Continued.)

Characteristic	Unmatched Patients		Propensity-Score–Matched Patients†	
	Hydroxychloroquine (N=811)	No Hydroxychloroquine (N=565)	Hydroxychloroquine (N=811)	No Hydroxychloroquine (N=274)
Azithromycin	486 (59.9)	127 (22.5)	486 (59.9)	102 (37.2)
Other antibiotic agent	604 (74.5)	305 (54.0)	604 (74.5)	183 (66.8)
Tocilizumab	58 (7.2)	12 (2.1)	58 (7.2)	9 (3.3)
Remdesivir	22 (2.7)	5 (0.9)	22 (2.7)	5 (1.8)
Initial vital signs — median (IQR)				
Systolic blood pressure — mm Hg	125 (111–139)	127 (111–144)	125 (111–139)	126 (110–138)
Diastolic blood pressure — mm Hg	75 (67–82)	76 (68–84)	75 (67–82)	74 (65–83)
Heart rate — beats/min	98 (86–111)	97 (83–109)	98 (86–111)	97 (84–108)
Oxygen saturation — %	94 (90–96)	96 (94–98)	94 (90–96)	94.5 (92–96)
Respiratory rate — breaths/min	20 (18–22)	18 (18–20)	20 (18–22)	19.5 (18–22)
Calculated Pao_2:FIO_2	223 (160–303)	360 (248–431)	223 (160–303)	273 (185–360)
Initial laboratory tests — median (IQR)‖				
D-Dimer — μg/ml	1.25 (0.76–2.28)	1.1 (0.59–2.35)	1.26 (0.76–2.29)	1.33 (0.66–2.45)
Ferritin — ng/ml	785 (420–1377)	481 (213–989)	777 (417–1370)	552 (283–1095)
Lactate dehydrogenase — U/liter	414 (322–546)	333 (246–448)	412 (321–544)	370 (273–515)
C-reactive protein — mg/liter	125 (75–199)	76 (20–150)	125 (74–199)	106 (48–183)
Procalcitonin — ng/ml	0.21 (0.11–0.53)	0.14 (0.09–0.39)	0.21 (0.11–0.53)	0.18 (0.10–0.45)
Neutrophil count per mm^3	5.06 (3.64–7.26)	4.53 (2.72–6.81)	5.05 (3.63–7.26)	4.95 (3.20–7.30)
Lymphocyte count per mm_3	0.94 (0.65–1.28)	1.02 (0.64–1.47)	0.95 (0.66–1.30)	0.98 (0.68–1.37)

* ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, FIO_2 fraction of inspired oxygen, HIV human immunodeficiency virus, IQR interquartile range, and Pao_2 partial pressure of arterial oxygen.
† Data for patients included in the propensity-score–matched analysis were multiply imputed.
‡ Data on race and ethnic group, as reported by the patient, were obtained from the clinical data warehouse.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ Chronic lung disease was defined as chronic obstructive pulmonary disease, asthma, or chronic bronchitis.
‖ In the unmatched analysis, data on the D-dimer level were missing for 291 patients, on the ferritin level for 168, on the lactate dehydrogenase level for 153, on the C-reactive protein level for 150, on the procalcitonin level for 121, on the neutrophil count for 33, and on the lymphocyte count for 33. Multiple imputation was used to account for missing data in the propensity-score–matched analysis.

Kaplan–Meier curves and Cox models that used the inverse-probability-weighting weights were reported.

We conducted a secondary analysis that used propensity-score matching and another that included the propensity score as an additional covariate. In the propensity-score matching analysis, the nearest-neighbor method was applied to create a matched control sample. Additional sensitivity analyses included the same set of analyses with the use of a different study baseline of 48 hours after arrival to the emergency department as well as analyses that defined the exposure as receipt of the first dose of hydroxychloroquine before study baseline only. Multiple imputation was used to handle missing data, and model estimates and standard errors were calculated with Rubin's rules.[11] The nonparametric bootstrap method was used to obtain 95% pointwise confidence intervals for the inverse-probability-weighted Kaplan–Meier curves. The statistical analyses were performed with the use of R software, version 3.6.1 (R Project for Statistical Computing).

RESULTS

CHARACTERISTICS OF THE COHORT

Of 1446 consecutive patients with Covid-19 who were admitted to the hospital between March 7 and April 8, 2020, a total of 70 patients were ex-

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Table 2. Associations between Hydroxychloroquine Use and the Composite End Point of Intubation or Death in the Crude Analysis, Multivariable Analysis, and Propensity-Score Analyses.

Analysis	Intubation or Death
No. of events/no. of patients at risk (%)	
Hydroxychloroquine	262/811 (32.3)
No hydroxychloroquine	84/565 (14.9)
Crude analysis — hazard ratio (95% CI)	2.37 (1.84–3.02)
Multivariable analysis — hazard ratio (95% CI)*	1.00 (0.76–1.32)
Propensity-score analyses — hazard ratio (95% CI)	
With inverse probability weighting†	1.04 (0.82–1.32)
With matching‡	0.98 (0.73–1.31)
Adjusted for propensity score§	0.97 (0.74–1.28)

* Shown is the hazard ratio from the multivariable Cox proportional-hazards model, with stratification according to sex, chronic lung disease, and body-mass index, and with additional adjustment for age, race and ethnic group, insurance, current smoking, past diagnoses, current medications, vital statistics, and laboratory tests on presentation. The analysis included all 1376 patients.

† Shown is the primary analysis with a hazard ratio from the multivariable Cox proportional-hazards model with the same strata and covariates with inverse probability weighting according to the propensity score. The analysis included all the patients.

‡ Shown is the hazard ratio from a multivariable Cox proportional-hazards model with the same strata and covariates with matching according to the propensity score. The analysis included 1085 patients (811 who received hydroxychloroquine and 274 who did not).

§ Shown is the hazard ratio from a multivariable Cox proportional-hazards model with the same strata and covariates, with additional adjustment for the propensity score. The analysis included all the patients.

cluded from this study because they had already had intubation or death, were discharged after inpatient admission, or were directly admitted to alternative facilities within 24 hours after presentation to the emergency department. Thus, 1376 patients were included in the analysis (Fig. 1).

Over a median follow-up of 22.5 days, 346 patients (25.1%) had a primary end-point event (166 patients died without being intubated, and 180 were intubated). At the time of data cutoff on April 25, a total of 232 patients had died (66 after intubation), 1025 had survived to hospital discharge, and 119 were still hospitalized (only 24 of whom were not intubated) (Table S1 in the Supplementary Appendix).

Of the 1376 patients, 811 (58.9%) received hydroxychloroquine (median duration of treatment, 5 days) and 565 (41.1%) did not. Among the patients who received hydroxychloroquine, 45.8% received it in the 24 hours between their presentation to the emergency department and the start of study follow-up, and 85.9% received it within 48 hours after presentation to the emergency department. The timing of the first dose of hydroxychloroquine after presentation to the medical center is shown in Figure S3. The distribution of the patients' baseline characteristics according to hydroxychloroquine exposure is shown in Table 1, both in the unmatched and propensity-score–matched analytic samples. In the unmatched sample, hydroxychloroquine exposure differed according to age group, sex, race and ethnic group, body-mass index, insurance, smoking status, and current use of other medications. Hydroxychloroquine-treated patients had a lower Pao_2:Fio_2 at baseline than did patients who did not receive hydroxychloroquine (median, 233 vs. 360 mm Hg). In addition to the 27 patients listed in Table 1 who received remdesivir according to compassionate use, 30 patients in the study cohort were enrolled in randomized, blinded, placebo-controlled trials of that investigational agent or of sarilumab.

The distribution of the estimated propensity scores for receipt of hydroxychloroquine among patients who did and did not receive hydroxychloroquine is shown in Figure S1. The odds ratios (with 95% confidence intervals) for receipt of hydroxychloroquine according to all the variables included in the propensity-score model are shown in Table S2. The C-statistic of the propensity-score model was 0.81. In the matched analytic sample, 811 patients were exposed to hydroxychloroquine and 274 were not exposed. The differences between hydroxychloroquine and pretreatment variables were attenuated in the propensity-score–matched samples as compared with the unmatched samples (Table 2 and Fig. S2).

STUDY END POINTS

Among the 1376 patients included in the analysis, the primary end point of respiratory failure developed in 346 patients (25.1%); a total of 180 patients were intubated, and 166 died without intubation. In the crude, unadjusted analysis, patients who had received hydroxychloroquine were more likely to have had a primary end-point event than were patients who did not (hazard ratio, 2.37; 95% CI, 1.84 to 3.02) (Table 2). In the primary multivariable analysis with inverse probability weighting according to the propensity score, there was no significant association between hydroxychloroquine use and the composite primary end point (hazard ratio, 1.04; 95% CI, 0.82 to 1.32) (Fig. 2).

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There was also no significant association between treatment with azithromycin and the composite end point (hazard ratio, 1.03; 95% CI, 0.81 to 1.31).

Additional multivariable propensity-score analyses yielded similar results (Table 2). Multiple additional sensitivity analyses, including analyses that used a different baseline at 48 hours after presentation and analyses with treatment defined as receipt of the first dose of hydroxychloroquine before study baseline, showed similar results (Table S3).

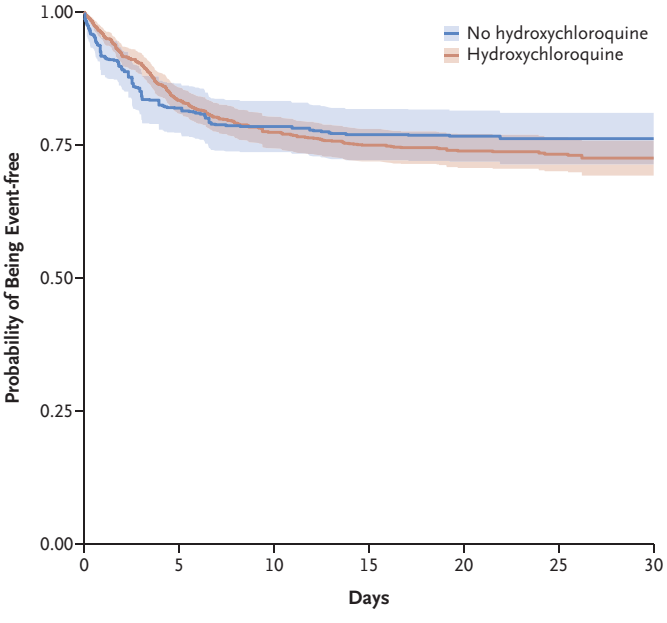

Figure 2. Freedom from Composite End Point of Intubation or Death.
The shaded areas represent pointwise 95% confidence intervals.

DISCUSSION

In this analysis involving a large sample of consecutive patients who had been hospitalized with Covid-19, the risk of intubation or death was not significantly higher or lower among patients who received hydroxychloroquine than among those who did not (hazard ratio, 1.04; 95% CI, 0.82 to 1.32). Given the observational design and the relatively wide confidence interval, the study should not be taken to rule out either benefit or harm of hydroxychloroquine treatment. However, our findings do not support the use of hydroxychloroquine at present, outside randomized clinical trials testing its efficacy.

As we noted in the introduction, the findings from an early study showing a benefit of hydroxychloroquine in 26 patients who had been treated in French hospitals are difficult to interpret, given the small size of that study, the lack of a randomized control group, and the omission of 6 patients from the analysis.[6] A clinical trial testing two doses of chloroquine in patients with Covid-19 planned to include 440 patients but was halted after 81 patients had been enrolled because of excessive QTc prolongation and an indication of higher mortality in the high-dose group (in which patients received 600 mg twice daily for 10 days) than in the low-dose group (in which patients received 450 mg daily for 4 days after an initial dose of 450 mg administered twice on the first day).[12]

Two small, randomized trials from China have been reported. Physicians in Wuhan randomly assigned 62 patients with mild illness to either the control group (in which patients could receive supplemental oxygen, unspecified antiviral agents, antibiotic agents, and immune globulin, with or without glucocorticoids) or the experimental group (in which patients also received 400 mg of hydroxychloroquine daily). This report has not yet been fully peer-reviewed, but results were posted to the MedRxiv website for public comment.[13] Investigators reported a faster mean time to clinical recovery (resolution of fever and cough and improvement on chest radiography) in the experimental group than in the control group. Four patients (all in the control group) had progression to severe infection. A small, randomized trial involving 30 patients in Shanghai reported on outcomes in patients treated with 400 mg of hydroxychloroquine daily for 5 days, as compared with a control group in which patients received "conventional treatment only."[14] This trial showed that by day 7, a total of 86% of the patients in the hydroxychloroquine-treated group and 93% of those in the control group had negative results on viral throat swabs. All the patients in this trial also received aerosolized interferon alfa by nebulizer.

A randomized clinical trial is the best approach to determine whether benefit can be ascribed to any given therapeutic intervention because this trial design minimizes the two major problems inherent in observational studies: unmeasured confounding and bias. With the analytic approaches we used in this examination of

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our observational cohort, we have tried to minimize possible confounding in a variety of ways.

In the main analysis, a multivariable regression model with inverse probability weighting according to the propensity score, there was no significant association between hydroxychloroquine use and the risk of intubation or death. We also performed a series of analyses using several propensity-score approaches. Findings were similar in multiple sensitivity analyses. The consistency of the results across these analyses is reassuring. In our analysis, we adjusted for likely confounders, including age, race and ethnic group, body-mass index, diabetes, underlying kidney disease, chronic lung disease, hypertension, baseline vital signs, Pao_2:Fio_2, and inflammatory markers of the severity of illness. Despite this extensive adjustment, it is still possible that some amount of unmeasured confounding remains. Additional limitations of our study include missing data for some variables and potential for inaccuracies in the electronic health records, such as lack of documentation of smoking and coexisting illness for some patients. Nonetheless, we used contemporary methods to deal with missing data to minimize bias. Finally, the single-center design may limit the generalizability of these results.

Clinical guidance at our medical center has been updated to remove the suggestion that patients with Covid-19 be treated with hydroxychloroquine. In our analysis involving a large sample of consecutive patients who had been hospitalized with Covid-19, hydroxychloroquine use was not associated with a significantly higher or lower risk of intubation or death (hazard ratio, 1.04; 95% CI, 0.82 to 1.32). The study results should not be taken to rule out either benefit or harm of hydroxychloroquine treatment, given the observational design and the 95% confidence interval, but the results do not support the use of hydroxychloroquine at present, outside randomized clinical trials testing its efficacy.

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