TREATING COVID-19 WITH HYDROXYCHLOROQUINE (TEACH): A MULTICENTER, DOUBLE-BLIND, RANDOMIZED CONTROLLED TRIAL IN HOSPITALIZED PATIENTS

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Abstract

**Background:**

Effective therapies to combat COVID-19 are urgently needed. Hydroxychloroquine (HCQ) has *in vitro* antiviral activity against SARS-CoV-2, but the clinical benefit of HCQ in treating COVID-19 is unclear. Randomized controlled trials are needed to determine the safety and efficacy of HCQ for the treatment of hospitalized patients with COVID-19.

**Methods:**

We conducted a multicenter, double-blind, randomized clinical trial of HCQ among patients hospitalized with laboratory confirmed COVID-19. Subjects were randomized in a 1:1 ratio to HCQ or placebo for five days and followed for 30 days. The primary efficacy outcome was a severe disease progression composite endpoint (death, ICU admission, mechanical ventilation, ECMO, and/or vasopressor use) at day 14.

**Results:**

A total of 128 patients were included in the intention-to-treat analysis. Baseline demographic, clinical, and laboratory characteristics were similar between HCQ (N=67) and placebo (N=61) arms. At day 14, 11 (16.4%) subjects assigned to HCQ and 6 (9.8%) subjects assigned to placebo met the severe disease progression endpoint, but this did not achieve statistical significance (P=.350). There were no significant differences in COVID-19 clinical scores, number of oxygen-free days, SARS-CoV-2 clearance, or adverse events between HCQ and placebo. HCQ was associated with a slight increase in mean corrected QT interval, an increased D-dimer, and a trend towards an increased length of stay.
Conclusions:

In hospitalized patients with COVID-19, our data suggest that HCQ does not prevent severe outcomes or improve clinical scores. However, our conclusions are limited by a relatively small sample size, and larger randomized controlled trials or pooled analyses are needed.

**Key words:** COVID-19, SARS-CoV-2, hydroxychloroquine, randomized controlled trial.
Introduction

Coronavirus disease 2019 (COVID-19) is an acute pneumonia syndrome caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and is currently responsible for over 25 million infections and 850,000 deaths worldwide [1]. Effective therapies combating SARS-CoV-2 are urgently needed to prevent severe outcomes related to COVID-19.

The antimalarial and immunomodulatory drug hydroxychloroquine (HCQ) is one candidate to treat SARS-CoV-2. In vitro data shows that HCQ has antiviral effects against SARS-CoV-2 [2]; Possible mechanisms include decreased SARS-CoV-2 binding due to HCQ interference with terminal glycosylation of the angiotensin-converting enzyme 2 (ACE2) receptor [3] and increased endosomal pH interfering with proteolytic enzymes involved in SARS-CoV-2 processing [4]. In addition to a direct antiviral effect, HCQ also reduces in vitro T-cell activation [5] and cytokine expression [6] during SARS-CoV-2 infection, leading to the hypothesis that HCQ may decrease the cytokine storm associated with severe outcomes in COVID-19. Hydroxychloroquine is approved by the US Food and Drug Administration (FDA) for treatment of lupus and rheumatoid arthritis and has an established safety profile for those conditions [7, 8].

As the COVID-19 pandemic intensified, HCQ was widely adopted as off-label treatment and was recommended in treatment guidelines by the Chinese government [9], some US hospital systems [10], and professional societies [11]. On March 28, 2020, HCQ gained emergency use authorization (EUA) by the FDA for the treatment of COVID-19 [12]. Despite early adoption of HCQ as COVID-19 therapy, the existing clinical data do not clearly show whether HCQ is beneficial, has no effect, or causes harm in hospitalized patients with COVID-19. Early in the pandemic, a small (N=36) open-label, non-randomized study in France suggested that HCQ decreased viral shedding [13], and a randomized trial (N=62) in China suggested a possible time-to-recovery benefit from HCQ in addition to standard care.
More recently, large retrospective inpatient COVID-19 cohorts from US (N=2,541) and French (N=3,737) health systems suggested a mortality benefit associated with use of HCQ [10, 15]. Conversely, other large observational studies of hospitalized patients with COVID-19 failed to show improved outcomes associated with HCQ administration [16, 17], and found that HCQ treatment of COVID-19 is associated with an increased risk of QT interval prolongation [18, 19]. In light of these data, the Infectious Diseases Society of America published guidelines recommending the use of HCQ for COVID-19 be limited to clinical trials [20], and the FDA rescinded the EUA on June 15, 2020 [21]. A recent meta-analysis concluded that the evidence regarding HCQ therapy for COVID-19 is "very weak and conflicting" [22], and a call for well-designed randomized controlled trials (RCT) is prominent in the literature.

We performed a multicenter, placebo-controlled, RCT during the peak of the pandemic in New York to evaluate the efficacy and safety of HCQ in hospitalized patients with COVID-19. We hypothesized that HCQ is superior to placebo in preventing severe outcomes among hospitalized COVID-19 patients.

Methods

Regulatory

This study was approved by the New York University Grossman School of Medicine Institutional Review Board (s20-00463), Bellevue STAR Research Review Committee (STUDY00002403), and the SUNY Downstate Institutional Review Board (Study #1590355). The NYU Langone COVID-19 Data Safety and Monitoring Board (DSMB) provided oversight throughout the study period. Clinicaltrials.gov registration (NCT04369742) was initiated by the study team April 15, 2020, but due to administrative delays during COVID-19, the NYU Office of Science and Research submitted the registration to Clinicaltrials.gov on April 27, 2020.
**Study Sites**

We enrolled patients at NYU Langone Health (Tisch Hospital and Kimmel Pavilion, NYU Langone—Brooklyn Hospital, and NYU Winthrop Hospital), NYC Health and Hospitals/Bellevue Hospital Center (BHC), and State University of New York (SUNY) Downstate Medical Center.

**Trial Design**

Enrolled subjects were randomized 1:1 to study drug or placebo and followed for 30 days. Randomization was stratified by age (>60 years old) and study site. Subjects and investigators were blinded to the treatment assignment, but in cases of rapid COVID-19 progression meeting our primary endpoint, or at the request of the treating physician, we allowed for subject unblinding. Subject visits were performed by study personnel at baseline, day 6 (or day of discharge if discharge occurred before day 6), day 14, and day 30. Vital signs, laboratory results, clinical scores, and monitoring for the primary outcome was performed by electronic medical record (EMR) review. Concomitant antibacterial therapy and off-label agents for SARS-CoV-2 were allowed. The protocol was amended to allow for co-enrollment in other COVID-19 therapeutic trials and for the enrollment of children and pregnant women. Adverse events (AE) were captured throughout the study period; AEs of interest were defined by the study team and included common AEs attributed to HCQ [23]. The full protocol is provided in the supplementary materials.

**Population**

To identify potential participants, the EMR at each site was screened daily to identify hospitalized patients with a positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR). To enhance recruitment at NYU Langone Health, providers could refer patients directly from the EMR as part of admission orders (Figure S1). In addition to a positive RT-PCR within 72 hours of enrollment, inclusion criteria required at least one COVID-19 symptom (e.g., fever, cough, dyspnea, nausea, diarrhea, myalgia, anosmia,
dysgeusia) and the subject’s (or legally authorized representative’s) written informed consent. We excluded subjects who met the primary endpoint (admitted to the intensive care unit [ICU], mechanical ventilation, extracorporeal membrane oxygenation [ECMO], and/or vasopressor use) at enrollment, had received any doses of HCQ or chloroquine (CQ) within 30 days, were unable to take oral medications, were allergic to HCQ or CQ, had a baseline corrected QT (QTc) interval >500 milliseconds (ms), were on concomitant therapy with antiarrhythmic medications (flecainide, amiodarone, digoxin, procainamide, propafenone, thioridazine, or pimozide), and who had a history of cardiac arrest, retinal disease, or glucose-6-phosphate dehydrogenase deficiency.

**Study Drug**

Hydroxychloroquine sulfate 200mg tablets (Amneal Brand, Ahmedabad, India) were provided by the New York State Department of Health. The placebo agent, calcium citrate 200mg tablets (Major Pharmaceuticals, Livonia, MI), was obtained by the NYU Langone Health Investigational Pharmacy. Dosing of both HCQ and calcium citrate was 400 mg (2 tablets) by mouth two times per day (day 1) and 200 mg (1 tablet) by mouth two times per day (days 2-5); the five-day course was based on *in vitro* projections to optimize HCQ tissue levels against SARS-CoV-2 [24]. If the subject was discharged prior to completing the five-day course, the remaining doses were provided for home therapy and compliance was assessed at the day 14 telephone follow-up.

**Outcomes**

The primary efficacy outcome was the proportion of subjects meeting a severe COVID-19 progression composite endpoint (death, ICU admission, mechanical ventilation, ECMO, and/or vasopressor use) at day 14. The primary safety outcome was the cumulative incidence of serious adverse events (SAE), grade 3 or 4 adverse events, and/or discontinuation of therapy at day 30.
Secondary clinical outcomes included changes in an 8-point ordinal COVID-19 clinical severity score (defined in Table 2), the primary composite outcome and mortality at day 30, hospital length of stay (LOS), fever-free days and oxygen-free days (defined as 7 [the maximum number of days with vital signs captured] minus the number of days with temperature ≥100.4 F or requiring supplemental oxygen). Secondary laboratory outcomes included SARS-CoV-2 viral clearance on nasopharyngeal PCR, clinically significant changes from baseline to follow-up (day 6, or day 3 if day 6 was unavailable) creatinine [25], hepatic and hematology labs [26], and changes in inflammatory markers (CRP, LDH, ferritin, interleukin-6) and coagulation factors (D-dimer) associated with severe COVID-19 [27, 28].

**Sample Size**

Based on early internal unpublished data from NYU Langone Health, the primary composite endpoint was estimated to occur in 30% of COVID-19 admissions. We aimed to detect a 10% reduction in the endpoint rate, to 20% in the HCQ arm. Using a two-sided Type I error rate of 0.05, 626 patients would need to be enrolled to provide 80% power to detect this difference. We began enrollment on April 17, 2020, but enrollment decreased substantially as COVID-19 admissions decreased across the region. After consideration with the DSMB, enrollment was paused across all sites on May 12, 2020, prior to achieving the desired sample size. COVID-19 admission numbers did not increase to an adequate number to resume enrollment.

**Statistical Analysis**

Data were summarized using mean, median, standard deviation, and range for continuous variables, and frequencies for categorical variables. The primary outcome was assessed using a chi-squared test comparing the proportion meeting the primary outcome by randomized treatment group. The secondary outcome of the 8-point ordinal COVID-19 severity score was assessed using the Wilcoxon rank-sum test. Primary analyses used the intention-to-treat (ITT) paradigm in which participants are classified according to their
randomized treatment assignment, regardless of treatment receipt or compliance. Secondary analyses assessed the safety population (those who receive any dose of study medication) and the per protocol population (those who received at least 80% of their assigned dose).

Results

Study Population

Between April 17 and May 12, 2020, we screened 724 hospitalized patients with a positive RT-PCR test for SARS-CoV-2 and randomized 128 patients, as outlined in Figure 1. The baseline characteristics of the study population are shown in Table 1. Treatment groups did not differ significantly with respect to age, gender, or ethnicity. Although our protocol was amended to allow enrollment of pediatric and pregnant subjects, the youngest participant was 19 years old and no pregnant patients were enrolled. Subjective fever (N=72, 56.2%), cough (N=86, 67.2%) and dyspnea (N=83, 64.8%) were the most common presenting symptoms with no statistically significant differences between subjects assigned to HCQ or placebo. Hypertension (N=74, 57.8%), obesity (N=46, 35.9%), and diabetes (N=41, 32%) were the most common comorbidities. Categories of body mass index (BMI) were significantly higher in the placebo arm than subjects receiving HCQ (chi-squared $P=.023$). Although 36 subjects (28.1%) reported a history of smoking, only 8 (6.2%) reported active smoking at enrollment. On baseline vital signs, one in three subjects had documented fever and nearly two thirds required oxygen supplementation, with no difference between HCQ or placebo in amount of oxygen needed or type of oxygen delivery device. Baseline laboratory values, radiography results, and COVID-19 ordinal severity scores were similar between participants assigned HCQ or placebo.
Outcomes

Primary and secondary outcomes by treatment group are shown in Table 2. Of 128 subjects in the ITT analysis, 17 (13.3%) met the primary efficacy composite endpoint (death, ICU admission, mechanical ventilation, ECMO, and/or vasopressor use) by day 14. In the HCQ arm, 11 (16.4%) subjects had severe disease progression, compared to 6 (9.8%) subjects assigned to placebo; the difference was not statistically significant ($P=.350$). The primary safety outcome was met by a similar proportion of subjects assigned to HCQ (N=23, 34.3%) and placebo (N=19, 31.1%) during the study period ($P=.620$). Similar to the ITT analysis, there were no statistically significant differences between HCQ and placebo in the primary outcomes using the safety or per-protocol analysis (Table S1), or when age stratified subgroups (≤60 and >60 years old) were assessed (Table S2).

Thirty-day mortality in the HCQ (N=7, 10.4%) and placebo (N=6, 9.8%) arms did not differ significantly ($P=1.00$). The mean number of fever-free and oxygen-free days was nearly identical between treatment arms. The average LOS was 9.75 (±10.3) days in HCQ and 6.80 (±5.92) days with placebo, a trend that approached statistical significance ($P=.053$). There were no significant differences in day 14 severity scores between HCQ and placebo ($P=.354$), with the majority of the cohort (N=88, 68.8%) having COVID-19 severity scores in the outpatient range (level 7 or 8). Ninety-five (74.2%) subjects improved their COVID-19 severity scores from baseline to day 14 (Figure 2), with no significant difference between HCQ or placebo ($P=.274$).

We did not observe an increase in acute kidney injury, hepatotoxicity, hypoglycemia, anemia or thrombocytopenia from HCQ compared to placebo. The mean change in QTc interval was significantly longer ($P=.029$) in patients treated with HCQ (16ms ±30.0) than placebo (2.1ms ±25.3) but there was no statistically significant difference between HCQ (N=3, 4.5%) and placebo (N=1, 1.6%) in follow-up QTc >500ms ($P=.680$). Inflammatory laboratory changes were similar between treatment arms except for an increase in D-dimer...
in subjects assigned HCQ (+800 ng/dL ±3550) compared to placebo (-288ng/dL ±1700) ($P=.047$). Follow-up SARS-CoV-2 RT-PCR was performed in 67 (52.3%) participants at a median of 6 (IQR 4) days, with 8 (11.9%) subjects assigned HCQ and 10 (16.4%) subjects assigned placebo achieving viral clearance ($P=.639$).

**Concomitant medications**

Data on concomitant antibacterial therapies, anticoagulation, off-label SARS-CoV-2 agents, and other COVID-19 clinical trials are shown in **Table 3**. Of the total study population, 30 (23.4%) subjects were taking azithromycin on admission or started azithromycin during the hospitalization. The majority (N=115, 89.8%) were on either prophylactic or therapeutic anticoagulation, with no difference between arms. Other off-label SARS-CoV-2 therapies were administered to 44 (34.4%) participants, most commonly zinc (N=17, 13.3%). Importantly, there were no statistically significant differences in the individual concomitant off-label SARS-CoV-2 therapies between the HCQ and placebo groups. One in five subjects was co-enrolled in another COVID-19 clinical trial during the study period, with comparable numbers in the HCQ (N=13, 19.5%) and placebo (N=13, 21.3%) arms ($P=.962$).

**Adverse Events**

Adverse events did not differ significantly between HCQ and placebo arms (**Table 4**). There were 122 separate AEs captured in 74 (58.7%) subjects during the study period, the majority of which (N=94, 77.0%) were mild to moderate in severity. Seven (10.4%) participants assigned to HCQ and 4 (6.6%) participants assigned to placebo had AEs deemed “possibly related” ($P=.639$) to study medication, and no AEs were reported as “definitely related” to study medication. The most common AE of interest was gastrointestinal complaints, with no significant difference between the number of HCQ (N=17, 25.4%) and placebo (N=10, 16.4%) subjects affected ($P=.305$). There were no arrhythmias or cardiac arrests in either treatment group.
Discussion

In this multicenter, double-blind, randomized controlled trial of non-ICU patients hospitalized with COVID-19, a five-day course of HCQ did not suggest improved outcomes or clinical scores at day 14 compared to placebo. There was a slightly increased QTc interval, an increased D-dimer, and an indication of an increased LOS for participants treated with HCQ compared to those treated with placebo. Adverse events were similar between HCQ and placebo groups. However, our findings are limited by a relatively small sample size due to a decrease in COVID-19 cases across the New York area.

Our results are concordant with recent large, randomized clinical trials examining the effect of HCQ in hospitalized COVID-19 patients. The RECOVERY trial randomized 1561 patients to HCQ and found no difference in mortality, but an increased LOS and risk of disease progression, when compared to 3155 patients assigned usual care [29]. Despite our smaller sample size, our findings also suggest a three day increase in LOS, on average, in the HCQ arm compared to placebo ($P=.053$). Additionally, our results are compatible with the World Health Organization (WHO) international COVID-19 therapeutic trial SOLIDARITY [30] and a recently published Brazilian multisite, open-label, RCT (N=504) that failed to show any benefit of HCQ compared to standard care for inpatients with COVID-19 [31]. Finally, our results are consistent with ORCHID, a US multisite trial (N=479) of COVID-19 hospitalized patients that stopped enrollment due to a lack of observed benefit of HCQ compared to placebo [32]. Our trial, in concordance with these RCTs, support the bedrock medical research principle that RCTs are needed to determine whether therapies are effective or—just as importantly—not beneficial, even in the midst of a pandemic; Despite in vitro activity, anecdotal success, and observational data suggesting benefit, data from well-designed RCTs are mounting that HCQ does not benefit patients hospitalized with COVID-19.
Patients assigned to HCQ in this study had a slight increase in QTc interval compared to placebo. This is consistent with observational studies showing QT prolongation is associated with HCQ use in COVID-19 [19]. However, the number of subjects (N=4, 3.1%) with QTc intervals that increased to a generally accepted clinically significant level (>500 ms) was not large enough to show any treatment-related differences. Interestingly, subjects on HCQ had a mean increase in D-dimer, while those assigned to placebo had a decreased D-dimer. The mechanism behind this finding is unclear, but D-dimer levels correlate with COVID-19 severity [33] and thrombosis in COVID-19 [34]. Although our sample size is limited with respect to the primary composite outcome, the increases in QTc interval, D-dimer, and the trend towards increased LOS may be subtle indicators that HCQ worsens disease in hospitalized COVID-19 patients.

Our trial had several limitations. First, the primary outcome rate was initially estimated at 30%, but likely as a result of improved COVID-19 care, the primary outcome occurred in only 13.3% of subjects at 14 days and 14.8% at 30 days. Secondly, the sample size did not meet enrollment targets due to the waning COVID-19 case numbers across the region; The number of COVID-19 hospitalizations in New York City peaked on April 6, 2020, at 1,724 daily admissions, but by the first enrollment in this trial (April 17, 2020), COVID-19 admissions had nearly halved to 902 per day, and continued rapidly falling during the study period [35]. Our difficulty enrolling during a declining epidemic was similar to trials during Ebola [36] and Zika [37] outbreaks, and poses the risk of overinterpreting the data. However, our negative findings are concordant with larger trials examining HCQ as therapy for COVID-19 [29-32], and our significant findings of a prolonged QTc, increased D-dimer and a trend towards increased LOS with HCQ treatment remain notable. Additionally, data pooling efforts are ongoing as part of the COVID-19 Collaborative Platform [38] and other established methods [39] to combine our data with other RCTs to increase statistical power. A third limitation was the use of calcium citrate as a placebo agent, which raises concerns of participant unblinding and unforeseen COVID-19 therapeutic effects. To mitigate these
concerns, we selected a formulation of calcium citrate that closely mimicked the size, color and characteristics of HCQ and the dose remained within the daily recommended dietary allowance [40]. Finally, our study did not enroll children or pregnant women. Therefore, our trial results are only relevant to the adult non-pregnant population hospitalized with COVID-19.

Conclusion

Therapies against SARS-CoV-2 are urgently needed to improve COVID-19 morbidity and mortality. This double blind, placebo-controlled, randomized trial did not suggest that HCQ is beneficial in preventing severe outcomes or improving clinical scores among non-ICU hospitalized patients with COVID-19. Treatment with HCQ was associated with a slight QTc interval prolongation, an increased D-dimer, and a trend towards an increased length of stay. However, our findings are limited due to a relatively small sample size and larger randomized trials are needed.
Footnotes

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Table 1: Baseline Characteristics by Treatment Group¹

| Demographics                      | Overall N = 128 | HCQ N = 67 | Placebo N = 61 | P    |
|-----------------------------------|----------------|------------|----------------|------|
| Age (years): mean (SD)            | 66.2 (16.2)    | 66.5 (16.4) | 65.8 (16.0)    | 0.804|
| Male sex                          | 76 (59.4)      | 45 (67.2)  | 31 (50.8)      | 0.089|
| Race/Ethnicity                    |                |            |                |      |
| Hispanic                          | 50 (39.1)      | 25 (37.3)  | 25 (41.0)      | 0.807|
| Non-Hispanic African American     | 26 (20.3)      | 15 (22.4)  | 11 (18.0)      | 0.695|
| Non-Hispanic Asian                | 10 (7.81)      | 3 (4.5)    | 7 (11.5)       | 0.253|
| Non-Hispanic white                | 41 (32.0)      | 23 (34.3)  | 18 (29.5)      | 0.694|
| Unknown                           | 1 (0.78)       | 1 (1.5)    | 0 (0)          | 1.000|
| Temperature (Fahrenheit)          |                |            |                |      |
| Afebrile (<100.4)                 | 86 (67.2)      | 46 (68.7)  | 40 (65.6)      | 0.855|
|                  |                  |                  |                  |
|------------------|------------------|------------------|------------------|
| **Febrile (≥100.4)** | 42 (32.8)        | 21 (31.3)        | 21 (34.4)        |
| **Oxygen Supplementation** |                  |                  |                  |
| Nasal cannula    | 62 (48.4)        | 28 (41.8)        | 34 (55.7)        | 0.162 |
| O2(L): mean (SD)$^2$ | 3.17 (1.57)      | 2.96 (1.79)      | 3.34 (1.36)      | 0.355 |
| High flow nasal cannula | 1 (0.8)          | 1 (1.5)          | 0 (0.0)          | 1.000 |
| Non-invasive ventilation (CPAP or BiPAP) | 1 (0.8)          | 1 (1.5)          | 0 (0.0)          | 1.000 |
| Non-rebreather   | 18 (14.1)        | 11 (16.4)        | 7 (11.5)         | 0.583 |
| **Body Mass Index (BMI)$^3$** |                  |                  | 0.023            |
| <20              | 8 (6.2)          | 56 (7.5)         | 3 (4.9)          |
| >=20 < 30        | 74 (57.8)        | 45 (67.2)        | 29 (47.5)        |
| >=30 <= 40       | 34 (26.6)        | 15 (22.4)        | 19 (31.3)        |
| >40              | 12 (9.4)         | 2 (3.0)          | 10 (16.4)        |
| **COVID-19 Symptoms** |                  |                  |                  |
| Cough            | 86 (67.2)        | 42 (62.7)        | 44 (72.1)        | 0.343 |
| Dyspnea/Shortness of Breath | 83 (64.8)        | 41 (61.2)        | 42 (68.9)        | 0.471 |
| Fever            | 72 (56.2)        | 36 (53.7)        | 36 (59.0)        | 0.672 |
| Fatigue          | 59 (46.1)        | 33 (49.3)        | 26 (42.6)        | 0.566 |
| Myalgia          | 33 (25.8)        | 13 (19.4)        | 20 (32.8)        | 0.127 |
| Diarrhea         | 34 (26.6)        | 17 (25.4)        | 17 (27.9)        | 0.905 |
| Nausea/Vomiting  | 22 (17.2)        | 11 (16.4)        | 11 (18.0)        | 0.994 |
| Abdominal pain   | 18 (14.1)        | 7 (10.4)         | 11 (18.0)        | 0.328 |
| Chest pain       | 17 (13.3)        | 7 (10.4)         | 10 (16.4)        | 0.466 |
| Headache         | 17 (13.3)        | 9 (13.4)         | 8 (13.1)         | 1.000 |
| Loss of sense of smell | 13 (10.2)        | 6 (9.0)          | 7 (11.5)         | 0.858 |
| Loss of sense of taste | 16 (12.5)        | 9 (13.4)         | 7 (11.5)         | 0.947 |
| Anorexia         | 16 (12.5)        | 6 (9.0)          | 10 (16.4)        | 0.316 |
| Sore Throat      | 12 (9.4)         | 5 (7.5)          | 7 (11.5)         | 0.635 |
| Rhinorrhea       | 7 (5.5)          | 5 (7.5)          | 2 (3.3)          | 0.515 |
| Nasal congestion | 6 (4.7)          | 4 (6.0)          | 2 (3.3)          | 0.763 |
### Symptom Duration

| Symptom Duration | Median (IQR) |
|------------------|--------------|
| Days since symptom onset | 7.00 (10.0) 6.50 (6.00) 7.00 (10.0) | 0.091 |

### Comorbidities

| Condition                                      | Other (37.2%) | Other (31.3%) | Other (26.2%) | p-value |
|------------------------------------------------|---------------|---------------|---------------|---------|
| Hypertension (HTN)                             | 74 (57.8%)    | 36 (53.7%)    | 38 (62.3%)    | 0.423   |
| Diabetes                                       | 41 (32.0%)    | 19 (28.4%)    | 22 (36.1%)    | 0.457   |
| Cardiovascular disease (non-HTN)               | 34 (26.6%)    | 21 (31.3%)    | 13 (21.3%)    | 0.279   |
| Asthma                                         | 20 (15.6%)    | 9 (13.4%)     | 11 (18.0%)    | 0.637   |
| Cancer                                         | 15 (11.7%)    | 8 (11.9%)     | 7 (11.5%)     | 1.000   |
| Hyperlipidemia                                 | 13 (10.2%)    | 8 (11.9%)     | 5 (8.2%)      | 0.684   |
| Chronic renal disease (non-dialysis)           | 10 (7.8%)     | 7 (10.4%)     | 3 (4.9%)      | 0.404   |
| COPD                                           | 9 (7.0)       | 5 (7.5)       | 4 (6.6)       | 1.000   |
| Cerebrovascular disease                        | 8 (6.2)       | 7 (10.4)      | 1 (1.6)       | 0.091   |
| HIV                                            | 7 (5.5)       | 5 (7.5)       | 2 (3.3)       | 0.515   |
| Chronic renal disease (dialysis)               | 4 (3.1)       | 2 (3.0)       | 2 (3.3)       | 1.000   |
| History of solid organ transplant              | 2 (1.6)       | 2 (3.0)       | 0 (0)         | 0.518   |
| Other                                          | 45 (35.2%)    | 19 (28.4%)    | 26 (42.6%)    | 0.133   |
| None of the above                              | 16 (12.5%)    | 8 (11.9%)     | 8 (13.1%)     | 1.000   |

### Smoking

| Smoking | Other (37.2%) | Other (31.3%) | Other (26.2%) | p-value |
|---------|---------------|---------------|---------------|---------|
| Active smoking | 8 (6.2%) | 5 (7.5%) | 3 (4.9%) | 0.819 |
| Past smoking    | 36 (28.1%) | 16 (23.9%) | 20 (32.8%) | 0.356 |
| Vaporizer use   | 1 (0.8%) | 1 (1.5%) | 0 (0) | 1.000 |

### Inhaler use

| Inhaler use | Other (37.2%) | Other (31.3%) | Other (26.2%) | p-value |
|-------------|---------------|---------------|---------------|---------|
| No inhaler  | 96 (75.0%)    | 54 (80.6%)    | 42 (68.9%)    |         |
| Yes, Albuterol only | 14 (10.9%) | 7 (10.4%) | 7 (11.5%) |         |
| Yes, Albuterol and other long acting inhalers | 18 (14.1%) | 6 (9.0%) | 12 (19.7%) |         |

### Electrocardiogram

| Electrocardiogram | Other (37.2%) | Other (31.3%) | Other (26.2%) | p-value |
|-------------------|---------------|---------------|---------------|---------|
| Corrected QT interval (Bazett formula) in milliseconds: mean (SD) | 441 (22.9) | 439 (23.2) | 443 (22.6) | 0.354 |
| Radiography |  |
|-------------|---|
| Chest X-Ray | 122 (95.3) 64 (95.5) 58 (95.1) 1.000 |
| Chest CT    | 11 (8.6) 6 (9.0) 5 (8.2) 1.000 |

| Radiography Results |  |
|---------------------|---|
| Opacities           | 83 (64.8) 41 (61.2) 42 (68.9) 0.471 |
| Consolidations      | 21 (16.4) 10 (14.9) 11 (18.0) 0.814 |
| Bilateral           | 95 (74.2) 47 (70.1) 48 (78.7) 0.368 |
| Unilateral          | 11 (8.6) 6 (9.0) 5 (8.2) 1.000 |
| None of the above   | 24 (18.8) 14 (20.9) 10 (16.4) 0.671 |

| COVID-19 severity score* | 0.777 |
|--------------------------|-------|
| 3: Hospitalized, on non-invasive ventilation or high-flow nasal cannula | 21 (16.4) 14 (20.9) 7 (11.5) |
| 4: Hospitalized, on supplemental oxygen | 62 (48.4) 26 (38.8) 36 (59.0) |
| 5: Hospitalized, not on O2, requiring ongoing medical care | 43 (33.6) 26 (38.8) 17 (27.9) |
| 6: Hospitalized, not on O2, not requiring ongoing care | 2 (1.6) 1 (1.5) 1 (1.6) |

| SARS-CoV-2 RT-PCR |  |
|-------------------|---|
| Nasopharyngeal    | 128 (100) 67 (100) 61 (100) 1.000 |
| Days prior to enrollment: median (IQR) | 1.00 (1.00) 1.00 (0.00) 1.00 (1.00) 0.184 |

| Laboratory results: mean (SD) |  |
|-------------------------------|---|
| Creatinine (mg/dL)            | 1.57 (2.36) 1.62 (2.54) 1.51 (2.16) 0.806 |
| AST (U/L)                     | 55.2 (65.8) 62.8 (86.0) 46.9 (30.6) 0.180 |
| ALT (U/L)                     | 44.9 (49.3) 45.7 (58.4) 44.0 (37.4) 0.846 |
| Glucose (mg/dL)               | 123 (54.7) 118 (48.3) 129 (60.9) 0.264 |
| WBC (K/µL)                    | 7.67 (4.54) 7.80 (4.98) 7.53 (4.03) 0.745 |
| Absolute Lymphocyte count (K/µL) | 1.35 (2.21) 1.43 (2.97) 1.27 (0.79) 0.682 |
| Hemoglobin (g/dL)             | 12.1 (1.97) 12.1 (2.21) 12.0 (1.69) 0.590 |
| Platelet count (K/µL)         | 239 (114) 238 (117) 240 (111) 0.911 |
|                      | Number    | Median (IQR)    | Number    | Median (IQR)    | Number    | Median (IQR)    | Statistic |
|----------------------|-----------|-----------------|-----------|-----------------|-----------|-----------------|-----------|
| D-dimer (ng/mL)      | 27        | 957 (1500)      | 782 (960) | 1160 (1940)     | 0.168     |                 |           |
| Ferritin (ng/mL)     | 27        | 1070 (2110)     | 944 (1030)| 1200 (2870)     | 0.514     |                 |           |
| Bilirubin (mg/dL)    | 27        | 0.77 (0.89)     | 0.81 (0.97)| 0.73 (0.79)     | 0.612     |                 |           |
| LDH (U/L)            | 27        | 373 (158)       | 370 (146) | 376 (171)       | 0.823     |                 |           |
| C-reactive protein (mg/L) | 27    | 99.0 (87.1)     | 92.6 (74.3)| 106 (99.4)      | 0.393     |                 |           |
| Interleukin-6 (pg/mL)| 27        | 17.1 (24.9)     | 18.0 (26.8)| 16.1 (22.5)     | 0.755     |                 |           |
| Interleukin-6 missing| 27        | 53 (41.4)       | 25 (37.3) | 28 (45.9)       | 1.000     |                 |           |

**Abbreviations:** HCQ, hydroxychloroquine; IQR, interquartile range; SD, standard deviation; RT-PCR, reverse transcriptase polymerase chain reaction; AST, aspartate aminotransferase; ALT alanine aminotransferase; U, units; WBC, white blood cell count; LDH, lactic acid dehydrogenase

1. Unless otherwise specified, data is presented as: number of subjects (%)
2. Liters of oxygen calculated for N=62 patients on nasal cannula
3. BMI categories differ between treatment groups using Chi-squared test ($P=0.023$)
4. Wilcoxon rank-sum test is used for COVID-19 score
Table 2. Primary and Secondary Outcomes by Treatment Group

|                                     | Overall  | HCQ     | Placebo | P     |
|-------------------------------------|----------|---------|---------|-------|
|                                     | N = 128  | N = 67  | N = 61  |       |
| **PRIMARY OUTCOMES**                |          |         |         |       |
| Severe disease composite (day 14)*  | 17 (13.3)| 11 (16.4)| 6 (9.8) | 0.350 |
| Death                              | 8 (6.2)  | 3 (4.5) | 5 (8.2) | 0.659 |
| ICU admission                      | 14 (10.9)| 9 (13.4)| 5 (8.2) | 0.452 |
| Mechanical ventilation             | 9 (7.0)  | 5 (7.5) | 4 (6.6) | 1.000 |
| ECMO                               | 0 (0)    | 0 (0)   | 0 (0)   | NA    |
| Vasopressor use                    | 6 (4.7)  | 3 (4.5) | 3 (4.9) | 1.000 |
| Unknown                            | 11 (8.6) | 7 (10.4)| 4 (6.6) | 0.639 |
| **Primary safety composite (day 30)** | 42 (32.8)| 23 (34.3)| 19 (31.1)| 0.620 |
| Unknown                            | 18 (14.1)| 11 (16.4)| 7 (11.5)| 0.783 |
| **SECONDARY OUTCOMES**             |          |         |         |       |
| Severe disease composite (D30)     | 19 (14.8)| 13 (19.4)| 6 (9.8) | 0.166 |
| Death                              | 18 (10.2)| 7 (10.4)| 6 (9.8) | 1.000 |
| ICU admission                      | 12 (9.4) | 9 (13.4)| 3 (4.9) | 0.153 |
| Mechanical ventilation             | 8 (6.2)  | 5 (7.5) | 3 (4.9) | 0.778 |
| ECMO                               | 0 (0)    | 0 (0)   | 0 (0)   | NA    |
| Vasopressor use                    | 4 (3.1)  | 2 (3.0) | 2 (3.3) | 1.000 |
| Lost to follow-up                  | 25 (19.5)| 14 (20.9)| 11 (18.0)| 0.853 |
| **COVID-severity score at day-14** |          |         |         | 0.354 |
| 1: Death                           | 8 (6.2)  | 3 (4.5) | 5 (8.2) |       |
| 2: Ventilator or ECMO              | 2 (1.6)  | 2 (3.0) | 0 (0)   |       |
| 3: Hospitalized, on NIV or high-flow nasal cannula | 9 (7.0)  | 7 (10.4)| 2 (3.3) |       |
| 4: Hospitalized, on supplemental oxygen | 5 (3.9)  | 4 (6.0)| 1 (1.6) |       |
| 5: Hospitalized, not on O2, ongoing medical care | 2 (1.6) | 2 (3.0) | 0 (0) |       |
6: Hospitalized, not on O2, not requiring ongoing care  | 3 (2.3)  | 1 (1.5)  | 2 (3.3)  

7: Outpatient, limitation on activities or home O2  | 31 (24.2)  | 13 (19.4)  | 18 (29.5)  

8: Outpatient, no limitation on activities  | 57 (44.5)  | 28 (41.8)  | 29 (47.5)  

Unknown  | 11 (8.6)  | 7 (10.4)  | 4 (6.6)  

30-day mortality  | 13 (10.2)  | 7 (10.4)  | 6 (9.8)  

Fever free days (T <100.4 F): mean (SD)  | 6.36 (1.13)  | 6.40 (0.94)  | 6.31 (1.33)  

O2 supplementation free days: mean (SD)  | 4.53 (2.41)  | 4.63 (2.44)  | 4.43 (2.40)  

Length of stay: mean (SD) 

Admission to discharge (days)  | 8.34 (8.59)  | 9.75 (10.3)  | 6.80 (5.92)  

Electrocardiogram changes* 

qT interval > 500 ms  | 4 (3.1)  | 3 (4.5)  | 1 (1.6)  

Corrected qT interval (Bazett formula) change from baseline (ms): mean (SD)  | 9.21 (28.5)  | 16.0 (30.0)  | 2.10 (25.3)  

No follow-up EKG  | 48 (37.5)  | 26 (38.8)  | 22 (36.1)  

Safety laboratory changes on follow-up* 

Creatinine >1.5x baseline  | 7 (5.5)  | 5 (7.5)  | 2 (3.3)  

AST >3x ULN (if baseline normal) or 1.5x baseline  | 11 (9.6)  | 7 (10.4)  | 4 (6.6)  

ALT >3x ULN (if baseline normal) or 1.5x baseline  | 7 (5.5)  | 3 (4.5)  | 4 (6.6)  

Platelet count decrease to <75 K/µL  | 6 (4.7)  | 5 (7.5)  | 1 (1.6)  

Bilirubin >1.5x ULN (if baseline normal) or 1.5x baseline  | 2 (1.6)  | 1 (1.5)  | 1 (1.6)  

Inflammatory laboratory changes on follow-up* 

Ferritin (ng/mL): mean (SD)  | -196 (1840)  | 9.56 (786)  | -378 (2420)  

C-reactive protein (mg/L): mean (SD)  | -22.3 (96.3)  | -19.9 (78.1)  | -24.9 (114)  

LDH (U/L): mean (SD)  | -21.9 (158)  | -2.65 (153)  | -45.1 (162)  

29
D-dimer ng/mL: mean (SD) | 301 (2870) | 836 (3550) | -288 (1700) | 0.047
Interleukin-6 (pg/nL): mean (SD) | 55.6 (195) | 85.8 (245) | 17.9 (98.7) | 0.251

**SARS-CoV-2 follow-up RT-PCR**

| Positive | 49 (38.3) | 29 (43.3) | 20 (32.8) | 0.299
| Interval (days) between positive tests: median (IQR) | 6 (4) | 6 (4) | 6 (3) | 0.674
| Negative | 18 (14.1) | 8 (11.9) | 10 (16.4) | 0.639
| Interval (days) between tests if neg: median (IQR) | 6 (3.5) | 8 (3) | 6 (4) | 0.51
| No follow-up PCR performed | 61 (47.7) | 30 (44.8) | 31 (50.8) | 0.612

**Abbreviations:** HCQ, hydroxychloroquine; SAE, serious adverse event; AE, adverse event; T, temperature; F, Fareinheit; SD, standard deviation, AST, aspartate aminotransferase; ALT, alanine aminotransferase; U, units, LDH, lactic acid dehydrogenase; RT-PCR, reverse transcriptase polymerase chain reaction; IQR, interquartile range

1Unless otherwise specified, data is presented as: number of subjects (%)

2Number of patients with composite endpoint is less than the sum of each category as some subjects achieved multiple components of the composite endpoint

3Primary safety composite: serious adverse event and/or grade 3 or 4 AE and/or discontinuation of therapy for any reason. N=8 (4 placebo;4 HCQ) of these endpoints were positive due to of nursing error (medication not provided on discharge) or the subject was unable to confirm outpatient compliance.

4Wilcoxon rank-sum test is used for COVID-19 score.

5Follow-up electrocardiogram performed at day 6 or, if discharged prior, on day of discharge

6Day 6 labs compared to baseline, if day 6 was not available day 3 labs were used to calculate. The number of patients with missing data for all laboratory measures did not differ significantly between HCQ and placebo arms.
Table 3. Concomitant Medications and Clinical Trial Co-enrollment by Treatment Group

|                             | Overall N = 128 | HCQ N = 67 | Placebo N = 61 | P     |
|-----------------------------|-----------------|------------|----------------|-------|
| Antibacterial agents        |                 |            |                |       |
| Azithromycin: n (%)         | 30 (23.4)       | 13 (19.4) | 17 (27.9)      | 0.357 |
| Ceftriaxone: n (%)          | 31 (24.2)       | 19 (28.4) | 12 (19.7)      | 0.348 |
| Anticoagulation             |                 |            |                |       |
| VTE prophylaxis*: n (%)     | 69 (53.9)       | 39 (58.2) | 30 (49.2)      | 0.463 |
| Therapeutic anticoagulation*: n (%) | 46 (35.9) | 22 (32.8) | 24 (39.3) | 0.535 |
| Antiplatelet agents*: n (%) | 38 (29.7)       | 25 (37.3) | 13 (21.3)      | 0.096 |
| Off-label COVID-19 therapies: n (%) | 41 (32.0) | 27 (40.3) | 14 (23.0) | 0.056 |
| Zinc                        | 18 (14.1)       | 13 (19.4) | 5 (8.2)        | 0.117 |
| Corticosteroids             | 13 (10.2)       | 7 (10.4)  | 6 (9.8)        | 1.000 |
| Tocilizumab                 | 5 (3.9)         | 3 (4.5)   | 2 (3.3)        | 1.000 |
| Lopinavir-Ritonavir         | 1 (0.8)         | 1 (1.5)   | 0 (0)          | 1.000 |
| Remdesivir                  | 1 (0.8)         | 1 (1.5)   | 0 (0)          | 1.000 |
| Co-enrollment in other trials: n (%) | 26 (20.3) | 13 (19.4) | 13 (21.3) | 0.962 |
| Drug                        | Subjects | Placebo | Experimental | p-value |
|-----------------------------|----------|---------|--------------|---------|
| Convalescent Plasma         | 17 (13.3)| 7 (10.4)| 10 (16.4)    | 0.466   |
| Clazakizumab                | 4 (3.1)  | 4 (6.0) | 0 (0)        | 0.153   |
| Remdesivir (ACTT-2)         | 1 (0.8)  | 0 (0)   | 1 (1.6)      | 0.962   |
| Anticoagulation (PROTECT study) | 3 (2.3)  | 2 (3.0) | 1 (1.6)      | 1.000   |

**Abbreviations:** HCQ, hydroxychloroquine; VTE, venous thromboembolism; ACTT-2,

Adaptive COVID-19 Treatment Trial 2

1. Unless otherwise specified, data is presented as: number of subjects (%)
2. Subcutaneous heparin two or three times per day or enoxaparin once per day
3. Intravenous heparin, subcutaneous enoxaparin twice daily, apixaban or rivaroxaban
4. Aspirin and/or clopidogrel
5. The PROTECT trial randomized patients to prophylactic or therapeutic anticoagulation
Table 4. Adverse Events (AE) by Treatment Group¹

|                                      | Overall N = 128 | HCQ N = 67 | Placebo N = 61 | P²  |
|--------------------------------------|-----------------|------------|----------------|-----|
| Total # of patients with AE (%)      | 74 (58.7)       | 38 (56.7)  | 36 (59.0)      | 0.933 |
| Total # of events                    | 122             | 63         | 59             |     |
| AE Severity                          |                 |            |                |     |
| Mild                                 | 49 (38.3)       | 22 (32.8)  | 27 (44.3)      | 0.252 |
| Mild: # of events                    | 68              | 30         | 38             |     |
| Moderate                             | 21 (16.4)       | 14 (20.9)  | 7 (11.5)       | 0.231 |
| Moderate: # of events                | 26              | 18         | 8              |     |
| Severe                               | 17 (13.3)       | 9 (13.4)   | 8 (13.1)       | 1.000 |
| Severe: # of events                  | 27              | 14         | 13             |     |
| Relatedness to study treatment       |                 |            |                |     |
| Possibly related                     | 11 (8.6)        | 7 (10.4)   | 4 (6.6)        | 0.639 |
| Possibly related: # of events        | 16              | 9          | 7              |     |
| AEs of interest                      |                 |            |                |     |
| GI symptoms¹                         | 27 (21.1)       | 17 (25.4)  | 10 (16.4)      | 0.305 |
| GI symptoms¹: # of events            | 29              | 18         | 11             |     |
| Rash                                 | 5 (3.9)         | 1 (1.5)    | 4 (6.6)        | 0.308 |
| Rash: # of events                    | 7               | 2          | 5              |     |
| Subjective Complaint          | 1 (2.3) | 1 (1.5) | 2 (3.3) | 0.934 |
|-----------------------------|---------|---------|---------|-------|
| Headaches: # of events      | 4       | 1       | 3       |       |
| Vision Changes\(^a\)        | 0       | 0       | 0       |       |
| Arrhythmia                  | 0       | 0       | 0       |       |
| Cardiac Arrest              | 0       | 0       | 0       |       |

\(^1\)Unless otherwise specified, data is presented as: number of subjects (%)

\(^2\)P values are calculated for the proportion of patients with AEs not number of events

\(^3\)Nausea, vomiting, diarrhea, and/or constipation

\(^4\)Subjective complaint (vision was not objectively assessed as part of the study)
Figure 1. Trial Flow Diagram

Screened (SARS-CoV-2 PCR+)
N = 764

Excluded
N = 833

Enrolled
N = 131

Excluded pre-randomization
N = 3

Randomized ITT analysis
N = 128

Allocation
HCQ
N = 67

Placebo
N = 61

Follow-up
Lost to follow up
Day 14 N=7
Day 30 N=14

Lost to follow up
Day 14 N=4
Day 30 N=11

Analysis
Safety analysis
N=63

Per protocol analysis
N=50

Safety analysis
N=59

Per-protocol analysis
N=50

*4 patients in HCQ arm did not receive study drug (2 voluntarily withdrew, 2 received HCQ outside of the study). 2 patients in placebo arm did not receive study drug (1 voluntarily withdrew, 1 developed arrhythmia).
**2 subjects who missed D14 visits were reached on D30, and 4 subjects with D30 follow-up were reached outside of the D30 protocol window but included in the analysis.
***Safety analysis = received any study medication; Per-Protocol = received at least 80% of assigned doses.
Figure 2. Changes in COVID-19 Ordinal Severity Scores by Treatment Group

A: Change in clinical score at day 14 by treatment assignment. No difference between HCQ and placebo by Wilcoxon Rank-Sum Test ($P=0.274$)

B: Proportion of subjects with COVID-19 ordinal clinical scores measured at baseline, day 3, day 6, day 14 and day 30; O2, oxygen.