**BACKGROUND – THE STUDY QUESTION?**

| Background | Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that is highly contagious, spreads rapidly, and causes mild to severe respiratory illness (COVID-19), including pneumonia, acute respiratory distress syndrome (ARDS), and death  
Chloroquine and hydroxychloroquine (HCQ) are anti-malarial agents with anti-inflammatory and immunomodulatory effects and have demonstrated potent *in vitro* activity against coronaviruses, including SARS-CoV-2  
On March 28, 2020, the US FDA issued an emergency use authorization to distribute chloroquine and HCQ from the Strategic National Stockpile for treatment of inpatients with COVID-19 who are not eligible for a clinical trial |
| --- |
| Previous trials | Currently, there is a lack of evidence for a definitive therapeutic agent in the prevention and treatment of COVID-19  
In a small (n=30), inpatient, randomized controlled trial (RCT), HCQ did not result in shorter time to viral clearance or improvement in clinical symptoms vs standard of care (SOC)  
A brief report of 100 patients with COVID-19 in China claimed that chloroquine was superior to SOC in time to clinical recovery and improved lung imaging, but no data, clinical information, or statistical analyses were provided  
A non-randomized, open-label study in France of 42 patients with COVID-19 showed reduced viral titers with hydroxychloroquine vs SOC, but there are many concerns with this paper, including exclusion of 23% of HCQ patients from analysis, no reporting of clinical outcomes, and a statement from the journal's sponsoring organization declaring that the paper does not meet their publishing standard  
A second open-label, unblinded study from the French group reported undetectable viral loads in 66 of 80 patients on day 7 after therapy with HCQ plus azithromycin, but lack of a comparator group and other study flaws severely limit interpretation  
In a pre-print, randomized, parallel-group trial of 62 inpatients with COVID-19, HCQ resulted in more clinical improvement of pneumonia, decreased cough duration, and shorter time to clinical recovery versus SOC  
A prospective cohort of 11 patients receiving an identical regimen of HCQ and azithromycin to the French groups observed that 80% still had positive COVID-19 nasopharyngeal swabs by days 5-6  
A third open-label, unblinded study from the French group of 1061 patients with COVID-19 reported virologic cure in 91.7% in 10 days and lower mortality with HCQ and azithromycin versus other regimens  
A pre-print, open-label, RCT of 150 patients in China with mild COVID-19 observed no difference in 28-day negative conversion rate of SARS-CoV-2 but greater decrease in CRP and symptoms with HCQ vs SOC in a post-hoc analysis adjusting for conjunctive antiviral agent use  
All of these studies had significant limitations, including different HCQ dosing regimens, variability in SOC, lack of comparator groups, unclear methodology, subjective outcomes, post-hoc analyses, lack of long-term outcome data, and/or lack of peer review  
Many RCTs of HCQ for COVID-19 treatment, pre-exposure prophylaxis, and post-exposure prophylaxis are currently underway throughout the world (n=97 from ClinicalTrials.gov) |
| Why this study? | Hydroxychloroquine has been one of the most discussed potential therapies for the treatment of COVID-19, and existing studies have interpretation-limiting flaws  
There is no difference in clinical outcomes between those who received HCQ for the treatment of COVID-19 within 48 hours of hospitalization and those who did not |

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## GENERAL STUDY OVERVIEW

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<td>Trial design</td>
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<td>Objectives</td>
<td>• To evaluate the clinical effectiveness of HCQ in preventing intensive care unit (ICU) admission or death</td>
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<td>• To assess HCQ effectiveness of preventing ARDS</td>
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<td>Enrollment</td>
<td>• Patients enrolled from four French tertiary care centers</td>
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<td>• Records from patients hospitalized between March 17-31, 2020 were screened for enrollment</td>
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## METHODS

### Inclusion criteria
- Aged 18 – 80 years
- PCR-confirmed SARS-CoV-2 infection
- Required oxygen by mask or nasal cannula

### Exclusion criteria
- Contraindication to HCQ (including dialysis)
- Receipt of HCQ prior to hospital admission
- Receipt of another experimental drug for COVID-19 within 48 hours of admission
- Organ failure requiring immediate ICU admission
- ARDS at admission
- Discharge from ICU to standard care
- Decision to stop active therapeutics made at admission
- Opposition to data collection by participant or representative

### Treatment Arms
- Initiation of HCQ (total daily dose 600mg) within 48 hours of admission
- No HCQ within 48 hours of admission

### Monitoring
- Start of follow-up (time zero) was time of hospital admission
- End of follow-up was death, discharge, or hospital day 7
- If transferred to another hospital, physicians were contacted for outcome data
- If unable to obtain outcomes, data were considered missing
- All patients receiving HCQ had an ECG before initiation and 3 – 5 days into therapy

### Primary Endpoints
- Composite of transfer to ICU within 7 days of inclusion and/or all-cause mortality
| **Secondary Endpoints** | • All-cause mortality at day 7  
• Incidence of ARDS (need for non-invasive ventilation with provision of positive airway pressure or invasive mechanical ventilation) | • Defined quantitative criteria for secondary endpoints  
• Liberal definition for ARDS  
• Did not follow SARS-CoV-2 PCRs; however, clinical importance of this outcome is unclear |
|---|---|---|
| **Statistical analyses** | • Inverse probability of treatment weighting (IPTW) approach was used to balance characteristics in treatment groups  
• Non-parsimonious multivariable logistic regression estimated each patient’s probability of receiving HCQ based on baseline characteristics  
• Model variables included age, gender, comorbidities, BMI, pregnancy, receipt of ACEIs or ARBs, time since symptom onset, and severity of disease at admission  
• Performed several sensitivity analyses: unweighted sample, trimmed analysis truncated at 5% of the extreme weights, and analysis that excluded patients who received HCQ >48h after admission  
• Planned subgroup analysis of patients with a better prognosis at admission (qSOFA <2) | • All statistical analyses were performed using R (v3.6.1 or later)  
• Variables for the model were specified *a priori* and included many known or suspected influencing factors in COVID-19 disease severity  
• Included variables were objectively and appropriately defined  
• Did not include treatment location into the model  
• In current uncertainty surrounding COVID-19, unknown if all confounders were accounted for in the model  
• All sensitivity and subgroup analyses were planned *a priori* |
| **RESULTS** | | |
| **Enrollment** | 181 total patients enrolled  
84 received HCQ within 48h of admission; 97 did not | 8 patients in control group received HCQ >48h after admission |
| **Baseline characteristics** | Median age: 60 years [IQR 52, 68]; 71.1% male  
Lower frequency of all comorbidities, except cirrhosis, in HCQ group  
Median delay between symptom onset and hospital admission: 7 days [IQR 5,10]  
Similar disease severity between groups:  
• Respiratory rate: 27 breaths/min HCQ vs 26 control  
• Oxygen saturation w/o oxygen: 92% HCQ vs 92% control  
• Oxygen flow requirements: 3 L/min HCQ vs 2 control  
• Lymphocyte count <500/mm^3: 7.2% HCQ vs 9.6% control  
• C-reactive protein (CRP) >40mg/L: 90.5% HCQ vs 81.9% control  
• >50% of lung affected on CT scan: 21.9% HCQ vs 12.1% control  
• In HCQ group, 20% also received azithromycin; 76% received amoxicillin/clavulanic acid  
• Roughly 96% of propensity scores fell in region of common support  
• Confusion at admission, CKD, heart failure, and cirrhosis were not included in final propensity score model as weighted standardized differences were >10% | Similar population compared to other reports and studies of COVID-19 disease  
HCQ group had less comorbidities vs control group, but these were adjusted for with IPTW  
Did not include fever as a baseline characteristic  
Included patients were moderately ill  
Small numbers in one or both groups resulted in exclusion of four potentially important prognostic variables from final propensity score model  
Did not detail "standard of care" and/or other concomitant medications outside of antibiotics in HCQ group; however, authors state patients did not receive any other drug, like antiviral and anti-inflammatory agents, including steroids |
| Primary Outcome | • In IPTW analysis, 20.5% in HCQ group vs 22.1% in control group experienced death or transfer to ICU for a RR of 0.93, 95% CI 0.48 – 1.81
• Sensitivity analyses demonstrated similar results
  • Unweighted analysis: RR 0.88, 95% CI 0.49 – 1.57
  • Trimmed analysis: RR 0.90, 95% CI 0.45 – 1.77
  • Exclusion of patients who received HCQ >48h after admission: RR 0.95, 95% CI 0.47 – 1.93
• Subgroup analysis of patients with better prognosis on admission (qSOFA <2) yielded similar results: RR 1.12, 95% CI 0.54 – 2.32
• No missing data for primary outcome
• Transfer to ICU was driver of composite outcome |

| Secondary Outcomes | • In IPTW analysis, 2.8% in HCQ group vs 4.6% in control group died from any cause at day 7 of hospitalization for a RR of 0.61, 95% CI 0.13 – 2.90
• 27.7% in HCQ group vs 24.1% in control group developed ARDS for a RR of 1.15, 95% CI 0.66 – 2.01
• Subgroup analysis of patients with better prognosis on admission (qSOFA <2) yielded similar results for both overall mortality, (RR 1.09, 95% CI 0.15 – 7.76) and ARDS (RR 1.31, 95% CI 0.71 – 2.44)
• Low mortality rate compared to other studies and reports; this may be explained by the short length of follow-up
• Small numbers for all-cause mortality may limit interpretation
• Only 2 missing data points for ARDS incidence
• No follow up performed beyond 7 days |

| Adverse Effects | • In HCQ group, 9.5% of patients required HCQ discontinuation due to ECG changes at a median of 4 days [IQR 3, 9]
• 7 had QTc prolongation of >60 ms (1 QTc >500 ms)
• 1 patient receiving no other QTc-prolonging medications experienced first-degree AV block after 2 days of HCQ
• 1 patient in control group who received HCQ 5 days after admission was transferred to the ICU 2 days later and developed left bundle branch block after receiving lopinavir/ritonavir
• Similar QTc prolongation rates at similar time points as other studies of HCQ for COVID-19; EKG monitoring not performed in patients not on HCQ so no comparison can be made
• Use of HCQ resulted in significant adverse effects in a sizable portion of the study population
• Data on adverse events in the control group were not provided for comparison |

| AUTHORS’ CONCLUSIONS | • HCQ did not reduce ICU admissions, death, or development of ARDS at hospital day 7 versus SOC in hospitalized patients with hypoxemic COVID-19 pneumonia
• While reduction in viral titer was not included as an outcome, the chosen, robust clinical outcomes in this study are more clinically relevant
• High dose HCQ in elderly patients and frequent drug interactions may result in potential severe adverse effects like sudden cardiac death and arrhythmia
• The negative clinical results argue against widespread use of HCQ in patients with COVID-19 |
GENERALIZABILITY/CRITIQUE/DISCUSSION

- HCQ has been one of the most widely discussed and controversial potential therapies for COVID-19 with widespread adoption across the world
- Strong statistical methods helped strengthen this retrospective, observational study, but small numbers in some factors limited the final propensity score model, and potential unmeasured confounders may bias results
- Unlike other studies, SOC did not include other investigational therapies for COVID-19 including antivirals and anti-inflammatory agents
- Study evaluated early initiation of HCQ in inpatients with moderate to severe COVID-19 disease, but elevated CRP levels on admission suggest that treatment may not have been initiated early enough
- Short follow-up duration likely resulted in observed low mortality rate and limited conclusions of HCQ’s effect on this outcome
- While chosen clinical outcomes were appropriate, additional clinical outcomes of interest were lacking
- Significant adverse events were observed in roughly 10% of patients receiving HCQ, calling into question the safety of this therapy even with short-term use
- Given the above discussion, hydroxychloroquine may not be useful in improving clinical outcomes for hospitalized patients with COVID-19; results from ongoing RCTs are needed to confirm these findings

References