Mahévas M, Tran V-T, Roumier M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalised for COVID-19 infection and requiring oxygen: results of a study using routinely collected data to emulate a target trial. April 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.04.10.20060699v1.full.pdf Accessed April 17, 2020.

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)[1] • 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[2] • 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[3] • 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[4] • 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[5] • 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[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[7] • 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[8] • 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
Null Hypothesis	• 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

GENERAL STUDY OVERVIEW		
	Summary	Critique
Funding	• None	
Trial design	• Retrospective, emulated-target trial	• "Randomization" of observational data via statistical methods to control for unmatched treatment groups
Objectives	• To evaluate the clinical effectiveness of HCQ in preventing intensive care unit (ICU) admission or death • To assess HCQ effectiveness of preventing ARDS	
Enrollment	• Patients enrolled from four French tertiary care centers • Records from patients hospitalized between March 17-31, 2020 were screened for enrollment	• Multi-center study
METHODS		
Inclusion criteria	• Aged 18 – 80 years • PCR-confirmed SARS-CoV-2 infection • Required oxygen by mask or nasal cannula	• Included patients with at least moderate disease severity • Unclear why patients >80 years were not included
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	• Other experimental drugs for COVID-19 included tocilizumab, lopinavir-ritonavir, and remdesivir only • Renal replacement therapy is not a known contraindication to short term use of HCQ but may be a risk factor for severe disease • Excluded patients with more severe disease at admission • Did not exclude pregnant patients
Treatment Arms	• Initiation of HCQ (total daily dose 600mg) within 48 hours of admission • No HCQ within 48 hours of admission	• Evaluated early initiation of therapy as opposed to late initiation • Used a higher total daily dose than malarial dosing
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	• Minimized time-dependent bias with a standardized time zero • Long-term data were not provided as end of follow-up was day 7 of hospital admission • Thorough follow-up with outcomes data
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 anti-viral 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

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