

Hydroxychloroquine/Chloroquine for the Treatment of Hospitalized Patients with COVID-19: An Individual Participant Data Meta-Analysis

Leon Di Stefano, MS¹; Elizabeth L. Ogburn, PhD¹; Malathi Ram, PhD²; Daniel O. Scharfstein, ScD³; Tianjing Li, MD, PhD, MS⁴; Preeti Khanal, BS⁵; Sheriza N. Baksh, PhD, MPH⁶; Nichol McBee, MPH⁵; Joshua Gruber, MSPH⁵; Marianne R. Gildea, BSN, MS^{5,7}; Neil A. Goldenberg, MD, PhD^{8,9,10}; Yussef Bennani, MD, MPH^{11,12}; Samuel M. Brown, MD, MS^{13,14}; Whitney R. Buckel, PharmD¹⁵; Meredith E. Clement, MD^{11,12}; Mark J. Mulligan, MD, FIDSA^{16,17}; Jane A. O'Halloran, MD, PhD¹⁸; Adriana M. Rauseo, MD¹⁸; Wesley H. Self, MD, MPH¹⁹; Matthew W. Semler, MD²⁰; Todd Seto, MD²¹; Jason E. Stout, MD, MHS²²; Robert J. Ulrich, MD¹⁶; Jennifer Victory, RN, CCRC²³; Barbara E. Bierer, MD^{24,25}; Daniel F. Hanley, MD⁵; Daniel Freilich, MD²⁶; for the Pandemic Response COVID-19 Research Collaboration Platform for HCQ/CQ Pooled Analyses

¹Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

²Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

³Division of Biostatistics, Department of Population Health Sciences, University of Utah School of Medicine, Salt Lake City, Utah

⁴University of Colorado Denver, Anschutz Medical Campus, Denver, Colorado

⁵Division of Brain Injury Outcomes, Johns Hopkins School of Medicine, Baltimore, Maryland

⁶Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

⁷Now with FHI 360, Durham, North Carolina

⁸Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, Maryland

⁹Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland

¹⁰Johns Hopkins All Children's Institute for Clinical and Translational Research, Johns Hopkins All Children's Hospital, St. Petersburg, Florida

¹¹Louisiana State University Health Sciences Center, New Orleans, Louisiana

¹²University Medical Center, New Orleans, New Orleans, Louisiana

¹³Division of Pulmonary and Critical Care Medicine, Intermountain Medical Center, Murray, Utah

¹⁴University of Utah, Salt Lake City, Utah

¹⁵Pharmacy Services, Intermountain Healthcare, Murray, Utah

¹⁶Department of Medicine, Division of Infectious Diseases and Immunology, New York University Grossman School of Medicine, New York, New York

¹⁷Vaccine Center, New York University Grossman School of Medicine, New York, New York

¹⁸Department of Medicine, Washington University School of Medicine, Saint Louis, Missouri

¹⁹Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

²⁰Division of Allergy, Pulmonary and Critical Care Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

²¹Department of Medicine, University of Hawaii John A. Burns School of Medicine, Honolulu, Hawaii

²²Division of Infectious Diseases and International Health, Duke University Medical Center, Durham, North Carolina

²³Bassett Research Institute, Bassett Medical Center, Cooperstown, New York

²⁴Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts

²⁵Harvard Medical School, Boston, Massachusetts

²⁶Department of Internal Medicine, Division of Infectious Diseases, Bassett Medical Center, Cooperstown, New York

Corresponding Author:

Daniel Freilich, MD, Bassett Medical Center, 1 Atwell Road, Cooperstown, NY 13326
(daniel.freilich@bassett.org).

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Key Points

Question: Does hydroxychloroquine/chloroquine benefit hospitalized patients with COVID-19, overall or within prespecified subgroups?

Findings: In this individual participant data meta-analysis of 770 hospitalized COVID-19 patients across 8 clinical trials, we did not find evidence of a benefit of hydroxychloroquine/chloroquine, measured by a 7-point ordinal COVID-19 severity score at 28-35 days post-enrollment, in the pooled study population. We also found no substantial treatment effect heterogeneity among prespecified patient subgroups.

Meaning: This study supports the consensus that hydroxychloroquine/chloroquine should not be used to treat hospitalized patients with COVID-19.

Abstract

Importance: Results from observational studies and randomized clinical trials (RCTs) have led to the consensus that hydroxychloroquine (HCQ) and chloroquine (CQ) are not effective for COVID-19 prevention or treatment. Pooling individual participant data (IPD), including unanalyzed data from trials terminated early, enables further investigation of the efficacy and safety of HCQ/CQ.

Objective: To assess efficacy of HCQ/CQ in patients hospitalized with COVID-19, both overall and in prespecified subgroups.

Data Sources: ClinicalTrials.gov was searched multiple times in May-June 2020. Principal investigators of US-based RCTs evaluating HCQ/CQ in hospitalized COVID-19 patients were invited to collaborate in this IPD meta-analysis.

Study Selection: RCTs in which: (1) HCQ/CQ was a treatment arm; (2) patient informed consent and/or individual study IRB approval allowed for data sharing; (3) principal investigators/their institutions signed a data use agreement for the present study; and (4) the outcomes defined in this study were recorded or could be extrapolated.

Data Extraction and Synthesis: Wherever possible, harmonized de-identified data were collected via a common template spreadsheet sent to each principal investigator, then shared via a secure online data sharing platform to create a pooled data set. When this was not possible, individual study data were harmonized and merged manually. Data were analyzed by fitting a prespecified Bayesian ordinal regression model and standardizing the resulting predictions.

Main Outcome(s) and Measure(s): 7-point ordinal scale, measured between day 28 and 35 post-enrollment.

Results: Eight of 19 trials met eligibility criteria and agreed to participate. Patient-level data were available from 770 participants (412 HCQ/CQ vs 358 control). Baseline characteristics were similar between groups. We found no evidence of a difference in ordinal scores between days 28 and 35 post-enrollment in the pooled patient population (odds ratio, 0.97; 95% credible interval, 0.76-1.24; higher favors HCQ/CQ), and no convincing evidence of meaningful treatment effect heterogeneity among prespecified subgroups. Adverse event and serious adverse event rates were numerically higher with HCQ/CQ vs control (0.39 vs 0.29 and 0.13 vs 0.09 per patient, respectively).

Conclusions and Relevance: The findings of this IPD meta-analysis reinforce those of individual RCTs that HCQ/CQ is not efficacious for treatment of COVID-19 in hospitalized patients.

Introduction

During the COVID-19 pandemic Delta and Omicron variant surges, US daily deaths again reached 1,000-2,000, reinforcing the need for effective therapeutics. Early in the pandemic, hydroxychloroquine (HCQ) and chloroquine (CQ) received a Food and Drug Administration (FDA) Emergency Use Authorization (EUA) for treatment of hospitalized COVID-19 patients, and the drugs were administered empirically and recommended in some guidelines.^{1,2} Supportive efficacy data relied on inconsistent results from preclinical studies^{3,4} and small uncontrolled trials.^{5,6} Based in part on these early data, an estimated 42% of hospitalized COVID-19 patients in the US received HCQ in March 2020.⁷

Subsequently, most retrospective-observational studies of HCQ/CQ in hospitalized COVID-19 patients found no evidence of benefit, and possibly higher mortality, with concerns about toxicities.⁸⁻¹⁹ Results from at least 5 randomized clinical trials (RCTs) became available in spring/summer 2020; all showed no evidence of benefit, and most showed adverse safety signals.^{18,20-23} In light of these results, most principal investigators discontinued enrollment in HCQ/CQ arms of their trials. Consequently, adequate power to reach robust conclusions regarding efficacy and safety of HCQ/CQ was no longer attainable for many incomplete trials; moreover, effect estimates in published trials were accompanied by wide confidence intervals. Nevertheless, at least 11 additional RCTs published later in the pandemic found similar results.²⁴⁻³⁴

The purpose of this study was to ensure utilization of data from unpublished RCTs evaluating HCQ/CQ by combining them with published data, and to synthesize evidence on HCQ/CQ efficacy and safety in hospitalized COVID-19 patients, overall and in subpopulations of interest, by conducting an individual participant data (IPD) meta-analysis.

Methods

Trials Selection Summary

The Trial Innovation Network, funded by the National Center for Advancing Translational Sciences, partnered with the COVID-19 Collaboration Platform to promote coordination among research groups running similar trials. The team contacted principal investigators of COVID-19 RCTs registered on ClinicalTrials.gov on April 30, 2020, and encouraged uploading study protocols to the COVID-19 Collaboration Platform (CCP) repository (<http://covidcp.org>). The platform, initiated with the goal of sharing protocols to facilitate collaboration, aims to combine data or aggregate evidence from similar studies to increase efficiency and precision.

One respondent (Bassett) had independently initiated a collaboration registry effort and performed systematic searches of ClinicalTrials.gov on May 9, 2020, and May 21, 2020, using search words “COVID-19” and “hydroxychloroquine” or “chloroquine,” and study status of “recruiting.”

Trials from the Bassett search and CCP repository were aggregated. Additional outreach by investigators occurred in June 2020 to studies located at Clinical and Translational Science Awards Program institutions (eFigure 1 in the Supplement). This combined list was the primary driver for study selection, with augmentation and refinement by additional systematic ClinicalTrials.gov searches through June 2020.

US-based RCTs of HCQ/CQ to treat patients with SARS-CoV-2 infection were eligible for inclusion if patient informed consent and/or individual study IRB approval allowed data sharing; study institutions signed a data use agreement for the present study; the outcomes as defined in this study were recorded or could be extrapolated; and trialists agreed to participate. We excluded trials in non-hospitalized patients, trials not registered on ClinicalTrials.gov, trials without enrollment, and international trials to

avoid data sharing regulatory delays. We decided to focus on inpatient studies. No individual-level exclusion criteria were imposed beyond those employed by each study.

Data Collection and Harmonization

A common data harmonization tool, including a data dictionary with definitions and encodings of variables, example data, and deidentification functions for dates and ages consistent with Health Information Portability and Accountability Act requirements, was used by 7 trial teams to create data sets that were uploaded to the data repository Vivli (<https://www.vivli.org>) and then downloaded by the CCP team. ORCHID trial data were downloaded from the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) and manually harmonized by the CCP team. Queries about missing, unusual, or inconsistent data were resolved via direct contact with studies' principal investigators and, in some cases, manual chart review.

Outcomes

The primary outcome was clinical improvement measured on a 7-point ordinal scale with levels (1) death; (2) hospitalized, on mechanical ventilation or extracorporeal membrane oxygenation (ECMO); (3) hospitalized, on non-invasive ventilation (BiPAP/CPAP and/or high-flow oxygen); (4) hospitalized, requiring oxygen; (5) hospitalized, not requiring oxygen; (6) not hospitalized, with limitation; (7) not hospitalized, without limitations. We prespecified an outcome window of day 28-30 post-enrollment, which was broadened to day 28-35 after data collection due to missingness. Differences in the primary outcome were assessed using proportional odds ratios.

Secondary outcomes included hospital length of stay, need for mechanical ventilation, and 28-35-day mortality. Safety outcomes included rates of overall adverse events (AEs) and serious adverse events

(SAEs), and rates of specific AEs and SAEs of interest: elevated liver function tests (LFTs), QTc prolongation, and arrhythmias.

Baseline and Post-Baseline Variables

From each trial, baseline variables included treatment assignment, age (5-year interval bins), sex, race and ethnicity, body mass index (BMI), symptom duration, mechanical ventilation status, ordinal score, and comorbidities (cerebrovascular disease, myocardial infarction, congestive heart failure, dementia, chronic obstructive pulmonary disease, asthma, hypertension, tumor, liver disease, diabetes, smoking, and vaping), as well as post-baseline (enrollment through day 28) azithromycin and corticosteroid use (eTable 1 in the Supplement).

Statistical Analysis

The primary outcome was analyzed in two ways. First, we fit a proportional odds model with treatment indicator as the sole covariate using the “polr” command in R (version 4.0.4). Second, we fit a Bayesian proportional odds regression model including a main effect for treatment; fixed effects for sex and baseline ordinal scale (disease severity); splines of age, BMI, and a number of baseline comorbidities; and random effects for baseline ordinal scale and study. The fixed and random effects were also interacted with treatment. All fixed regression coefficients were given uniform priors. Random effects were modeled as independent, with standard deviations given independent half-t priors with 3 degrees of freedom and scale 10. The model was fit using the R package “brms” (version 2.15). Missing baseline covariates were imputed using multiple imputation by chained equations, as implemented in the R package “mice” (version 3.12). Inferences were based on fitting the model separately to each imputed data set, then pooling posterior draws across the imputations. The model was used to obtain standardized estimates of the overall treatment effect, where standardization was with respect to the empirical distribution of the baseline covariates in the pooled study population.

Relative to the first approach, we employed the second approach to leverage covariates to produce more stable and accurate inferences, particularly in small subgroups.

The following subgroup analyses were prespecified: study; sex; age (≤ 29 , 30-49, 50-69, 70-79, 80+ years); disease severity as measured by baseline ordinal score (2, 3, 4, 5); and BMI (≤ 20 , 20-25, 25-30, 30-35, >35). Prespecified subgroup analyses based on Charlson score were replaced with a simple baseline comorbidities count (0, 1, 2, 3, ≥ 4) due to systematic missingness in component variables.

Subgroup analyses were conducted using the two approaches discussed above. For the first, a proportional odds model was fit separately within each subgroup. For the second, the Bayesian regression model above was used to obtain standardized subgroup estimates, where standardization was with respect to the empirical distribution of covariates within subgroups. We conducted a post-hoc subgroup analysis using quintiles of a baseline risk score given by the expected linear predictor for each study participant under the control condition, as per recommendations from Kent et al.³⁵

All-cause 28-35-day mortality was analyzed using the same approaches. Other secondary and safety outcomes were analyzed descriptively.

To assess the sensitivity of our conclusions to the choice of model and outcome window, we (1) repeated our analysis with weakly informative priors; (2) fit an expanded model including terms for assignment to an azithromycin arm and days between symptom onset and enrollment; (3) fit a version of the main model with no treatment interactions; (4) expanded and contracted outcome windows to 28-40 and 28-30 days, respectively; and (5) re-ran our analysis with a model fit only to ORCHID's data set, the largest of the 8 pooled trials. Sensitivity analyses (1-2) were prespecified while (3-5) were post hoc.

We also examined conditional interaction estimates in the Bayesian regression model, focusing on effects for individuals with covariates set at reference values (age 60, BMI 25, no baseline comorbidities, baseline ordinal score 5, and sex predictors set between male and female values).

Risk of Bias Assessment

Two investigators (T.L. and S.N.B.) assessed risk of bias associated with the effect of assignment to treatment on the primary outcome using Cochrane's Risk of Bias 2 tool,³⁶ with disagreements resolved through discussion (eTable 2 in the Supplement). This assessment was not used in the data synthesis.

Registration

This study, including its statistical analysis plan (SAP), was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42021254261)³⁷ prior to receiving patient data and amended prior to analyzing outcome data. The most significant amendment was broadening the primary outcome definition from days 28-30 to 28-35 post-enrollment to minimize missingness. Post-hoc changes to the analysis are shown in eTable 3 in the Supplement. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline for IPD analyses.

Results

Study Characteristics

Of 19 RCTs identified in our searches (18 from ClinicalTrials.gov; 1 from personal communication), 8 met final criteria for inclusion in our analysis (**Figure 1**): (1) ORCHID ([NCT04332991](#))¹⁸; (2) TEACH ([NCT04369742](#))²⁶; (3) HAHPS ([NCT04329832](#))^{27,38}; (4) WU352 ([NCT04341727](#)); (5) [NCT04344444](#); (6) OAHU-COVID19 ([NCT04345692](#)); (7) [NCT04335552](#); and (8) COVID MED ([NCT04328012](#)) (eTables 4, 5, and 6 in the Supplement).³⁹

HCQ was a treatment arm in all studies; CQ was an additional treatment arm in one study (WU352). Comparators were placebo (3 trials), azithromycin (2 trials), and standard/usual care (2 trials); WU352 compared HCQ and CQ with and without azithromycin. HCQ dosing was usually (7 studies) 400 mg orally twice daily on day 1 and 200 mg twice daily on days 2-5, totaling 2,400 mg. Three trials were blinded; 5 were open-label.

Risk of Bias Assessment

Risk of bias judgments are summarized for the primary outcome measurement in eTable 2 in the Supplement. Overall, ORCHID and COVID MED were rated “low risk,”; the other trials were rated “some concerns.”

Patient Characteristics

Among 770 patients with laboratory-confirmed SARS-CoV-2 infection, 412 were randomized to HCQ/CQ treatment (398 HCQ; 14 CQ) and 358 to the control group (**Table 1**). Enrollment was at a median of 6 days (IQR, 3-8 days) after symptom onset. Most patients initiated dosing on the enrollment day.

Key baseline demographics were reasonably balanced between HCQ/CQ and control populations: mean age was 57 vs 55 years, male sex 59% vs 56%, White race 48% vs 44%, mean BMI 31.6 vs 33.2, mean comorbidities 3.16 vs 3.05 per patient, and mean ordinal score 4.1 vs 4.1, respectively. Post-baseline use of corticosteroids was 14% vs 17% and of azithromycin 24.5% vs 30.2%, respectively. Six patients with BMI values <10 or >70 were deemed probable recording errors and treated as missing in primary and mortality analyses.

Primary Outcome: Pooled and Subgroup Analysis

The standardized proportional odds ratio (OR) for ordinal score at 28-35 days was 0.97 (95% credible interval [CrI], 0.76-1.24); the corresponding unadjusted proportional OR was 0.98 (95% CI, 0.75-1.28) (**Figure 2** and **Table 2**). These results are consistent with no effect of HCQ/CQ. We found no appreciable heterogeneity in estimated treatment-study interactions among the 8 studies (after adjusting for individual-level baseline covariates; eFigure 2 in the Supplement).

While there were no substantial effects of HCQ/CQ within any prespecified subgroup, we investigated potential trends across strata of baseline ordinal score and BMI (**Figure 3**). We examined corresponding conditional effect estimates and found insufficient evidence to conclude that an effect of HCQ/CQ on the primary outcome differs by BMI or baseline ordinal score, after adjusting for other baseline covariates. These and other conditional effect analyses are shown in eFigure 3 in the Supplement.

Mortality: Pooled and Subgroup Analysis

Mortality at 28-35 days was similar in HCQ/CQ vs control groups (10%, n = 43 HCQ/CQ vs 9%, n = 34 control; model-adjusted risk difference [RD], -0.01 [95% CrI, -0.04 to 0.02]; plug-in RD, -0.01 [95% CI, -0.06 to 0.04], where a positive RD favors HCQ/CQ) (**Figure 3**). Again, we observed no appreciable heterogeneity in treatment effect estimates across prespecified subgroups. On the RD scale, there was greater uncertainty about the effect of HCQ/CQ upon mortality for those with higher baseline risk scores. For those with low baseline risk scores, the model precisely predicts only small effects of HCQ/CQ (RD for the first group, -0.01 [95% CrI, -0.02 to 0.01]; second group, -0.01 [95% CrI, -0.02 to 0.01]; third group, 0.00 [95% CrI, -0.02 to 0.02]; fourth group, -0.01 [95% CrI, -0.05 to 0.03]; and fifth group, -0.03 [95% CrI, -0.15 to 0.07]) (**Figure 3**). Separate estimates of mortality at day 28-35

under control and HCQ/CQ are shown in eFigure 4 in the Supplement, with conditional effect analyses in eFigure 3.

Sensitivity Analyses

Our alternative models and outcome definitions produced qualitatively similar conclusions about overall and subgroup effects. Simpler models than the one we prespecified (removing interactions, adding weakly informative priors) had better leave-one-out cross-validation performance than our primary prespecified model, while the model fit only to ORCHID data performed worse than our primary model (eMethods in the Supplement). Our primary model fit without individual-level treatment-covariate interactions yielded an adjusted OR of 0.92 (95% CrI, 0.58 to 1.41) for the benefit of HCQ/CQ. Posterior predictive checks of our primary model indicated good in-sample fit (eFigure 5 in the Supplement).

Exploratory Analysis of Secondary and Safety Outcomes

There were similar rates of mechanical ventilation between enrollment and day 28 (20% [n = 82] HCQ/CQ vs 21% [n = 76] control). HCQ/CQ and control patients had a median post-enrollment hospital length of stay of 7 days.

Overall AE rates were numerically higher in the HCQ/CQ vs the control group (0.39 vs 0.29 per patient, respectively), as were overall SAE rates (0.13 vs 0.09 per patient). LFTs elevation AE rates were also numerically higher with HCQ/CQ (0.05 [n = 21] vs 0.01 [n = 4] per patient). QTc prolongation and arrhythmia AE and SAE rates were similar (**Table 2**).

Discussion

This IPD meta-analysis of 8 RCTs in 770 hospitalized COVID-19 patients comparing HCQ/CQ and control treatment confirms results of at least 16 published RCTs showing no benefit of HCQ/CQ.^{18,20–34} Neither the primary outcome measurement, ordinal scale at 28-35 days, nor the secondary outcome measurement, mortality at 28-35 days, was improved with HCQ/CQ in the pooled study population. We found no subgroup in which appreciable benefits could be observed for the primary outcome. Overall rates of AEs and SAEs, and elevated LFT AEs, but not QTc prolongation AEs, were higher with HCQ/CQ than controls.

This study adds value to the literature by synthesizing IPD from 8 RCTs, of which 7 were terminated early, 4 unpublished, and 4 published individually and/or in aggregate data meta-analyses (ORCHID, TEACH, HAHPS, and NCT04335552).^{18,26,27,38,39} To our knowledge, this is the first published meta-analysis of HCQ/CQ trials in hospitalized COVID-19 patients to use IPD rather than aggregate data. IPD meta-analyses such as that reported here offer the advantage of using a multilevel model to obtain relatively stable estimates of patient-level subgroup effects⁴⁰ that have only been minimally investigated in aggregate data meta-analyses.^{39,41,42} We are aware of only 4 additional published IPD meta-analyses for COVID-19 therapeutics (3 planned; 1 smaller one completed).^{43–46} Two meta-analyses planned to use IPD data to supplement aggregate data but could not obtain them.^{41,47}

At least 50 aggregate data meta-analyses evaluating HCQ/CQ in hospitalized COVID-19 patients have been published, with the overwhelming majority finding lack of evidence of convincing clinical benefit, and many finding worse clinical outcomes and increased AE rates.^{39,41} The results of our study are congruous with the thrust of HCQ/CQ studies thus far, which have showed equivocal preclinical efficacy and no convincing evidence of clinical efficacy, as well as adverse safety signals, in the overwhelming majority of retrospective-observational studies, RCTs, and meta-analyses.^{8–34}

ORCHID is the largest trial in this IPD meta-analysis, and represents 62% of our study sample. It was a double-blind, placebo-controlled trial of HCQ in 479 hospitalized COVID-19 patients.¹⁸ Median interval from symptoms onset was 5 days, similar to our pooled cohort. The primary outcome, the World Health Organization 14-day ordinal score, was similar between HCQ vs placebo (adjusted proportional OR, 1.02; 95% CI, 0.73-1.42), as was the 28-day score (adjusted proportional OR, 1.07; 95% CI, 0.54-2.09). No evidence of substantive benefit was reported for any subgroup. Overall AE (21% vs 16%), overall SAE (7% vs 5%), and QTc prolongation (5.9% vs 3.3%) rates were numerically higher with HCQ. Our safety results are similar, except for QTc prolongation. Our efficacy analysis targets a different estimand, but produced qualitatively similar conclusions. Our primary analysis produced a comparably precise estimate of the overall effect of HCQ on day 28-35 ordinal scale compared with a similar analysis using a model fit to ORCHID data alone (OR 1.00; CrI 0.79 to 1.26). Subgroup effects from the full-data model tended to be more precise than those from the ORCHID-only model.

Key study limitations included: First, we included trials with open-label designs and varying treatments (HCQ vs CQ; with and without azithromycin). Second, 6 studies had some risk of bias. Third, we pooled a limited set of studies because some principal investigators declined participation and we excluded international trials. Fourth, we made SAP modifications after PROSPERO registration. Fifth, our analysis combined HCQ and CQ arms; only 16 patients received CQ alone.

Conclusions

Our IPD meta-analysis confirms published results from retrospective-observational studies, RCTs, and aggregate data meta-analyses showing no evidence of efficacy, but concerning safety signals, for hydroxychloroquine (or chloroquine) use overall and in prespecified subgroups of hospitalized COVID-19 patients.

Author Contributions: Mr Di Stefano and Dr Freilich had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Di Stefano, Ogburn, Li, Bierer, Hanley, Freilich.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Di Stefano, Ogburn, Ram, Scharfstein, Li, Khanal, Baksh, McBee, Gruber, Bierer, Hanley, Freilich.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Di Stefano, Ogburn, Scharfstein, Li, Freilich.

Obtained funding: Hanley.

Administrative, technical, or material support: Khanal, Ram, McBee, Gildea, Freilich.

Supervision: Ogburn, Scharfstein, Bierer, Hanley, Freilich.

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Table 1. Participant Characteristics Overall and in Each Trial

	Overall (n = 770)		ORCHID (n = 479)		TEACH (n = 128)		HAHPS (n = 85)		WU352 (n = 30)	NCT04344444 (n = 20)		OAHU-COVID19 (n = 16)		NCT04335552 (n = 11)		COVID MED (n = 1)
	HCQ/CQ (n = 412)	Control (n = 358)	HCQ/CQ (n = 242)	Control (n = 237)	HCQ/CQ (n = 67)	Control (n = 61)	HCQ/CQ (n = 42)	Control (n = 43)	HCQ/CQ (n = 30)	HCQ/CQ (n = 15)	Control (n = 5)	HCQ/CQ (n = 10)	Control (n = 6)	HCQ/CQ (n = 6)	Control (n = 5)	Control (n = 1)
Sex, No. (%)																
Female	167 (41)	158 (44)	106 (44)	105 (44)	22 (33)	30 (49)	14 (33)	19 (44)	18 (60)	2 (13)	2 (40)	4 (40)	0 (0)	1 (17)	2 (40)	0 (0)
Male	244 (59)	200 (56)	135 (56)	132 (56)	45 (67)	31 (51)	28 (67)	24 (56)	12 (40)	13 (87)	3 (60)	6 (60)	6 (100)	5 (83)	3 (60)	1 (100)
Missing/unknown	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Race, No. (%)																
Black	95 (23)	71 (20)	58 (24)	57 (24)	14 (21)	11 (18)	0 (0)	1 (2)	18 (60)	5 (33)	2 (40)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
White	197 (48)	158 (44)	109 (45)	103 (43)	32 (48)	23 (38)	29 (69)	26 (60)	11 (37)	10 (67)	2 (40)	2 (20)	0 (0)	4 (67)	3 (60)	1 (100)
Multiple	3 (1)	3 (1)	2 (1)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)
Other ^a	107 (26)	113 (32)	73 (30)	74 (31)	14 (21)	18 (30)	10 (24)	13 (30)	1 (3)	0 (0)	0 (0)	8 (80)	6 (100)	1 (17)	2 (40)	0 (0)
Unavailable	10 (2)	13 (4)	0 (0)	0 (0)	7 (10)	9 (15)	3 (7)	3 (7)	0 (0)	0 (0)	1 (20)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ethnicity, No. (%)																
Hispanic	144 (35)	135 (38)	91 (38)	87 (37)	25 (37)	25 (41)	15 (36)	17 (40)	1 (3)	9 (60)	3 (60)	1 (10)	0 (0)	2 (33)	3 (60)	0 (0)
Not Hispanic	248 (60)	210 (59)	145 (60)	143 (60)	42 (63)	36 (59)	27 (64)	24 (56)	25 (83)	0 (0)	0 (0)	9 (90)	6 (100)	0 (0)	0 (0)	1 (100)
Unavailable	20 (5)	13 (4)	6 (2)	7 (3)	0 (0)	0 (0)	0 (0)	2 (5)	4 (13)	6 (40)	2 (40)	0 (0)	0 (0)	4 (67)	2 (40)	0 (0)
Age (5y bins), median (IQR)	55.0 (45.0- 70.0)	55.0 (45.0- 65.0)	55.0 (45.0- 65.0)	55.0 (40.0- 65.0)	65.0 (55.0- 75.0)	65.0 (55.0- 75.0)	55.0 (40.0- 65.0)	50.0 (40.0- 60.0)	55.0 (45.0- 60.0)	70.0 (62.5- 75.0)	65.0 (60.0- 65.0)	67.5 (56.3- 70.0)	45.0 (41.3- 56.3)	47.5 (41.3- 61.3)	55.0 (50.0- 60.0)	55.0 (55.0- 55.0)
BMI																
Median (IQR)	30.0 (25.7- 36.1)	31.4 (27.0- 37.2)	31.3 (26.4- 37.2)	31.1 (27.2- 36.5)	25.9 (22.9- 30.5)	29.3 (24.9- 35.9)	31.7 (26.6- 37.4)	36.3 (30.7- 41.0)	30.5 (28.0- 34.0)	27.7 (24.3- 34.1)	29.3 (25.4- 34.2)	28.8 (26.7- 34.2)	26.0 (24.0- 30.5)	33.6 (30.2- 36.4)	44.2 (34.5- 47.9)	37.9 (37.9- 37.9)
Missing, No. (%)	16 (4)	19 (5)	16 (7)	18 (8)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Baseline ordinal scale, No. (%)																
2: hosp, mech vent	23 (6)	25 (7)	13 (5)	19 (8)	0 (0)	0 (0)	7 (17)	6 (14)	0 (0)	0 (0)	0 (0)	3 (30)	0 (0)	0 (0)	0 (0)	0 (0)

	Overall (n = 770)		ORCHID (n = 479)		TEACH (n = 128)		HAHPS (n = 85)		WU352 (n = 30)	NCT04344444 (n = 20)		OAHU-COVID19 (n = 16)		NCT04335552 (n = 11)		COVID MED (n = 1)
	HCQ/CQ (n = 412)	Control (n = 358)	HCQ/CQ (n = 242)	Control (n = 237)	HCQ/CQ (n = 67)	Control (n = 61)	HCQ/CQ (n = 42)	Control (n = 43)	HCQ/CQ (n = 30)	HCQ/CQ (n = 15)	Control (n = 5)	HCQ/CQ (n = 10)	Control (n = 6)	HCQ/CQ (n = 6)	Control (n = 5)	Control (n = 1)
3: hosp, NIV	49 (12)	42 (12)	28 (12)	27 (11)	13 (19)	7 (11)	6 (14)	7 (16)	1 (3)	1 (7)	1 (20)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
4: hosp, supp ox	191 (46)	175 (49)	116 (48)	108 (46)	25 (37)	34 (56)	23 (55)	24 (56)	13 (43)	7 (47)	3 (60)	6 (60)	5 (83)	1 (17)	0 (0)	1 (100)
5: hosp, no ox	146 (35)	112 (31)	85 (35)	83 (35)	26 (39)	17 (28)	6 (14)	6 (14)	16 (53)	7 (47)	0 (0)	1 (10)	1 (17)	5 (83)	5 (100)	0 (0)
Missing	3 (1)	4 (1)	0 (0)	0 (0)	3 (4)	3 (5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (20)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Baseline ordinal scale (numeric)																
Mean (SD)	4.1 (0.8)	4.1 (0.8)	4.1 (0.8)	4.1 (0.9)	4.2 (0.8)	4.2 (0.6)	3.7 (0.9)	3.7(0.9)	4.5 (0.6)	4.4 (0.6)	3.8 (0.5)	3.5 (1.1)	4.2 (0.4)	4.8 (0.4)	5.0 (0.0)	4.0 (NA)
Missing, No. (%)	3 (1)	4 (1)	0 (0)	0 (0)	3 (4)	3 (5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (20)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Days between symptom onset and enrollment																
Median (IQR)	5.0 (3.0- 8.0)	6.0 (3.0- 8.0)	5.0 (3.0- 7.0)	5.0 (3.0- 7.0)	7.0 (3.0- 9.0)	7.0 (4.0- 14.0)	8.0 (5.3- 12.0)	9.0 (7.0- 11.0)	5.0 (3.3- 9.8)	2.0 (2.0- 5.5)	6.0 (2.0- 10.0)	4.5 (4.0- 6.5)	2.5 (0.5- 3.8)	NA	NA	7.0 (7.0- 7.0)
Missing, No. (%)	6 (1)	5 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (100)	5 (100)	0 (0)
Baseline comorbidity count																
Median (IQR)	3.0 (2.0- 4.0)	3.0 (2.0- 4.0)	3.0 (2.0- 4.0)	3.0 (2.0- 4.0)	3.0 (3.0- 4.0)	4.0 (3.0- 5.0)	2.0 (1.0- 2.0)	2.0 (1.0- 3.0)	3.0 (2.0- 4.0)	5.0 (4.0- 5.5)	3.0 (3.0- 4.0)	2.0 (2.0- 3.0)	2.0 (1.3- 4.3)	NA	NA	NA
Missing, No. (%)	16 (4)	15 (4)	3 (1)	2 (1)	3 (4)	2 (3)	4 (10)	5 (12)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (100)	5 (100)	1 (100)
Azithromycin use (at or before d28), No. (%)																
Not assigned, did not take	311 (75)	248 (69)	195 (81)	193 (81)	54 (81)	44 (72)	28 (67)	0 (0)	16 (53)	4 (27)	5 (100)	10 (100)	4 (67)	4 (67)	2 (40)	0 (0)
Not assigned, took	75 (18)	63 (18)	47 (19)	44 (19)	13 (19)	17 (28)	14 (33)	0 (0)	0 (0)	1 (7)	0 (0)	0 (0)	2 (33)	0 (0)	0 (0)	0 (0)
Assigned, took	26 (6)	45 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	42 (98)	14 (47)	10 (67)	0 (0)	0 (0)	0 (0)	2 (33)	3 (60)	0 (0)
Assigned, did not take	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Missing	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Concurrent corticosteroid use (at or before d28), No. (%)																
Yes	57 (14)	61 (17)	39 (16)	49 (21)	7 (10)	6 (10)	7 (17)	6 (14)	2 (7)	2 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

	Overall (n = 770)		ORCHID (n = 479)		TEACH (n = 128)		HAHPS (n = 85)		WU352 (n = 30)	NCT04344444 (n = 20)		OAHU-COVID19 (n = 16)		NCT04335552 (n = 11)		COVID MED (n = 1)
	HCQ/CQ (n = 412)	Control (n = 358)	HCQ/CQ (n = 242)	Control (n = 237)	HCQ/CQ (n = 67)	Control (n = 61)	HCQ/CQ (n = 42)	Control (n = 43)	HCQ/CQ (n = 30)	HCQ/CQ (n = 15)	Control (n = 5)	HCQ/CQ (n = 10)	Control (n = 6)	HCQ/CQ (n = 6)	Control (n = 5)	Control (n = 1)
Missing	6 (1)	5 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (100)	5 (100)	0 (0)
First dose received on day of enrollment, No. (%)																
Yes	386 (94)	324 (91)	241 (100)	225 (95)	50 (75)	51 (84)	41 (98)	31 (72)	29 (97)	13 (87)	5 (100)	6 (60)	6 (100)	6 (100)	5 (100)	1 (100)
Missing	6 (1)	12 (3)	0 (0)	9 (4)	4 (6)	2 (3)	1 (2)	1 (2)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: BMI, body mass index; HCQ/CQ, hydroxychloroquine or chloroquine; IQR, interquartile range; NIV, noninvasive ventilation (includes BiPAP/CPAP and/or high-flow oxygen).

^aIncludes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, and other. To protect participant privacy, ORCHID's data set grouped three of its race variables with low frequencies (American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander). For the sake of uniformity, we combined these groups and the "Other" category for the other studies as well.

Table 2. Primary, Secondary, and Safety Outcomes, Overall and by Trial

	Overall (n = 770)	ORCHID (n = 479)	TEACH (n = 128)	HAHPS (n = 85)	WU352 (n = 30)	NCT04344444 (n = 20)	OAHU-COVID19 (n = 16)	NCT04335552 (n = 11)	COVID MED (n = 1)	Missing							
Primary outcome: Ordinal scale improvement under HCQ/CQ at day 28-35^a																	
Model-standardized proportional OR (95% CrI)	0.97 (0.76 to 1.24)	0.96 (0.74 to 1.23)	1.00 (0.68 to 1.59)	0.92 (0.61 to 1.36)	1.01 (0.51 to 1.72)	0.83 (0.52 to 1.59)	0.76 (0.38 to 1.30)	1.27 (0.66 to 2.44)	1.26 (0.23 to 4.03)	NA							
Plug-in proportional OR (95% CI)	0.98 (0.75 to 1.28)	1.02 (0.73 to 1.43)	0.75 (0.35 to 1.60)	0.81 (0.36 to 1.81)	NA	0.31 (0.01 to 2.85)	0.33 (0.04 to 2.30)	1.38 (0.11 to 18.47)	NA	36 (4.7%)							
Secondary outcomes^a																	
Mortality at day 28-35 under HCQ/CQ vs control, model-standardized RD (95% CrI)	-0.01 (-0.04 to 0.02)	-0.01 (-0.04 to 0.02)	0.00 (-0.04 to 0.05)	-0.03 (-0.07 to 0.05)	0.00 (-0.02 to 0.03)	-0.02 (-0.07 to 0.04)	-0.04 (-0.12 to 0.02)	0.01 (-0.03 to 0.08)	0.01 (-0.16 to 0.09)	NA							
Mortality at day 28-35 under HCQ/CQ vs control, plug-in RD (95% CI)	-0.01 (-0.06 to 0.04)	0.00 (-0.05 to 0.06)	-0.01 (-0.16 to 0.14)	-0.12 (-0.26 to 0.02)	NA	0.13 (-0.37 to 0.64)	-0.20 (-0.58 to 0.18)	-0.08 (-0.73 to 0.57)	NA	36 (4.7%)							
	Control (n = 358)	HCQ/ CQ (n = 412)	Control (n = 237)	HCQ/ CQ (n = 242)	Control (n = 61)	HCQ/ CQ (n = 67)	Control (n = 43)	HCQ/ CQ (n = 42)	HCQ/ CQ (n = 30)	Control (n = 5)	HCQ/ CQ (n = 15)	Control (n = 6)	HCQ/ CQ (n = 10)	Control (n = 5)	HCQ/ CQ (n = 6)	Control (n = 1)	Missing
Days of hospitalization between enrollment and day 28 (median)	7	7	8	7	5	5	6	6.5	4	2	9	9	18	8.5	4.5	9	1
Patients on mechanical ventilation between enrollment and day 28, No. (%)	76 (21)	82 (20)	58 (24)	51 (21)	4 (7)	7 (10)	11 (28)	14 (35)	3 (10)	0 (0)	1 (7)	2 (33)	5 (50)	1 (25)	1 (17)	0 (0)	7

	Overall (n = 770)		ORCHID (n = 479)		TEACH (n = 128)		HAHPS (n = 85)		WU352 (n = 30)	NCT04344444 (n = 20)		OAHU-COVID19 (n = 16)		NCT04335552 (n = 11)		COVID MED (n = 1)	Missing
	Control (n = 358)	HCQ/ CQ (n = 412)	Control (n = 237)	HCQ/ CQ (n = 242)	Control (n = 61)	HCQ/ CQ (n = 67)	Control (n = 43)	HCQ/ CQ (n = 42)	HCQ/ CQ (n = 30)	Control (n = 5)	HCQ/ CQ (n = 15)	Control (n = 6)	HCQ/ CQ (n = 10)	Control (n = 5)	HCQ/ CQ (n = 6)	Control (n = 1)	Missing
Safety outcomes																	
Adverse events (AEs), count (per patient)	104 (0.29)	160 (0.39)	39 (0.16)	50 (0.21)	59 (0.97)	63 (0.94)	2 (0.05)	3 (0.07)	29 (0.97)	1 (0.20)	8 (0.53)	3 (0.50)	7 (0.70)	NA	NA	0	11
Serious adverse events (SAEs), count (per patient)	32 (0.09)	53 (0.13)	12 (0.05)	18 (0.07)	11 (0.18)	14 (0.21)	0	0	9 (0.30)	1 (0.25)	4 (0.27)	2 (0.33)	4 (0.40)	6 (1.20)	4 (0.67)	0	1
QTc prolongation AEs, count (per patient)	8 (0.02)	14 (0.03)	3 (0.01)	2 (0.01)	1 (0.02)	3 (0.04)	2 (0.05)	3 (0.07)	2 (0.07)	1 (0.20)	3 (0.20)	1 (0.17)	1 (0.10)	NA	NA	0	11
QTc prolongation SAEs, count (per patient)	1 (0.00)	1 (0.00)	0	0	0	1 (0.01)	0	0	0	0	0	1 (0.17)	0	NA	NA	0	11
Elevated LFTs AEs, count (per patient)	4 (0.01)	21 (0.05)	3 (0.01)	12 (0.05)	0	1 (0.01)	0	0	0	0	7 (0.47)	1 (0.17)	1 (0.10)	NA	NA	0	11
Elevated LFTs SAEs, count (per patient)	0	0	0	0	0	0	0	0	0	0	0	0	0	NA	NA	0	11
Arrhythmia AEs, count (per patient)	10 (0.03)	8 (0.02)	10 (0.04)	1 (0.00)	0	0	0	0	2 (0.07)	0	4 (0.27)	0	1 (0.10)	NA	NA	0	11
Arrhythmia SAEs, count (per patient)	3 (0.01)	1 (0.00)	3 (0.01)	0	0	0	0	0	0	0	1 (0.07)	0	0	NA	NA	0	11
Missingness in the primary outcome (ordinal scale between day 28-35)																	
Nonmissing primary outcome, No. (%)	342 (96)	392 (95)	237 (100)	242 (100)	47 (77)	50 (75)	42 (98)	42 (100)	27 (90)	5 (100)	15 (100)	6 (100)	10 (100)	4 (80)	6 (100)	1 (100)	NA

^aPositive odds ratios and risk differences favor HCQ/CQ over control. Abbreviations: 95% CrI, 95% credible intervals; HCQ/CQ, hydroxychloroquine or chloroquine; LFTs, liver function tests; NA, not applicable; OR, odds ratio; RD, risk difference.

Figure Legends

Figure 1. Trial Selection Process

^aTwo of the trials did not have study acronyms (only trial registration numbers). COVID MED indicates Comparison Of Therapeutics for Hospitalized Patients Infected With SARS-CoV-2 In a Pragmatic aDaptive randoMized Clinical Trial During the COVID-19 Pandemic; HAHPS, Hydroxychloroquine vs. Azithromycin for Hospitalized Patients With Suspected or Confirmed COVID-19; OAHU-COVID19, A Randomized, Controlled Clinical Trial of the Safety and Efficacy of Hydroxychloroquine for the Treatment of COVID-19 in Hospitalized Patients; ORCHID, Outcomes Related to COVID-19 Treated With Hydroxychloroquine Among In-patients With Symptomatic Disease; TEACH, Treating COVID-19 With Hydroxychloroquine; WU352, Washington University 352: Open-label, Randomized Controlled Trial of Hydroxychloroquine Alone or Hydroxychloroquine Plus Azithromycin or Chloroquine Alone or Chloroquine Plus Azithromycin in the Treatment of SARS CoV-2 Infection.

Figure 2. Primary Outcome Data by Treatment Group

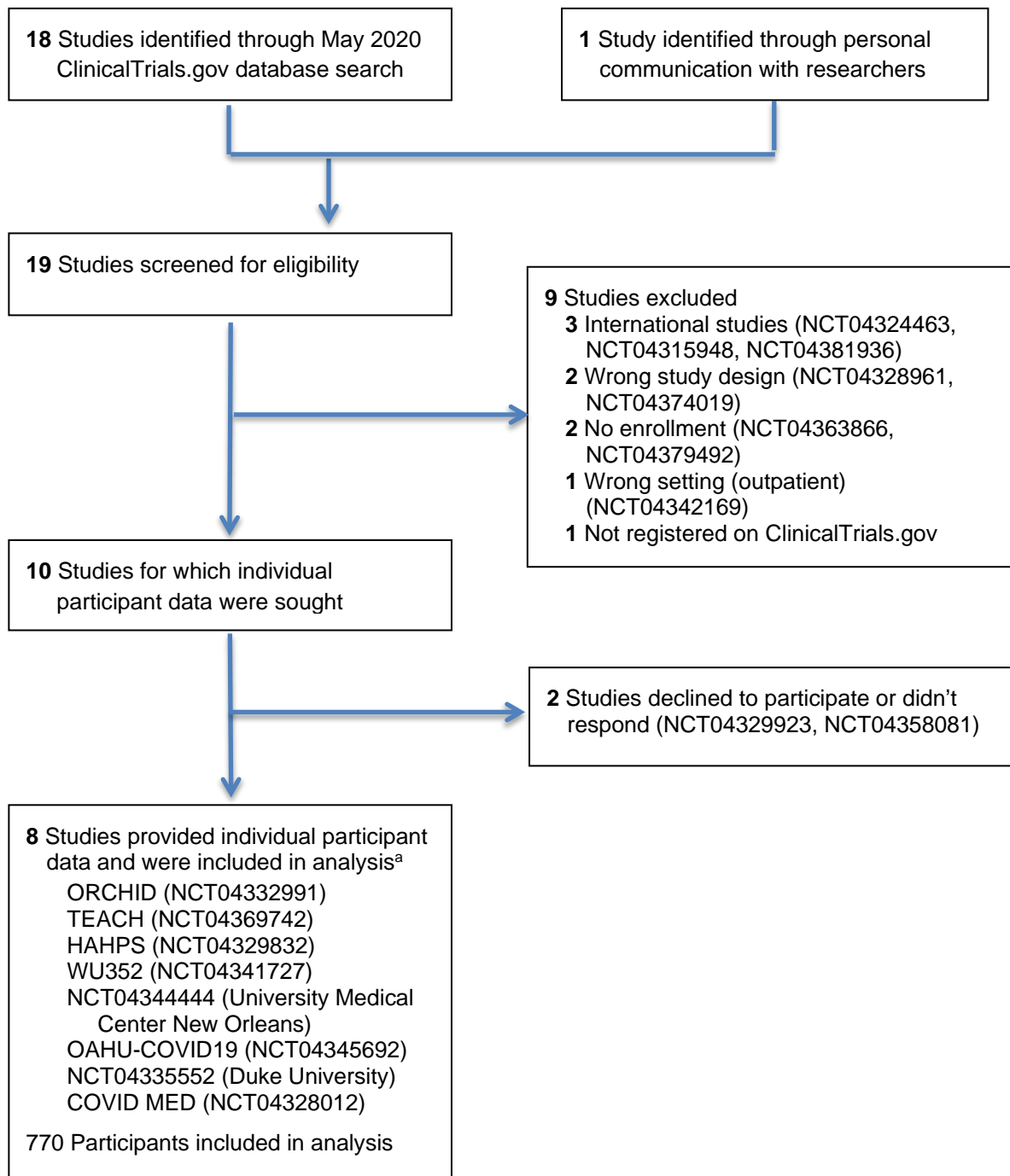
Scores were defined as: (1) death; (2) hospitalized, on mechanical ventilation or ECMO; (3) hospitalized, on non-invasive ventilation (BiPAP/CPAP and/or high-flow oxygen); (4) hospitalized, requiring oxygen; (5) hospitalized, not requiring oxygen; (6) not hospitalized, with limitation; (7) not hospitalized, without limitations. HCQ/CQ indicates hydroxychloroquine or chloroquine.

Figure 3. Subgroup Analysis of Differences in Outcomes at Days 28-35

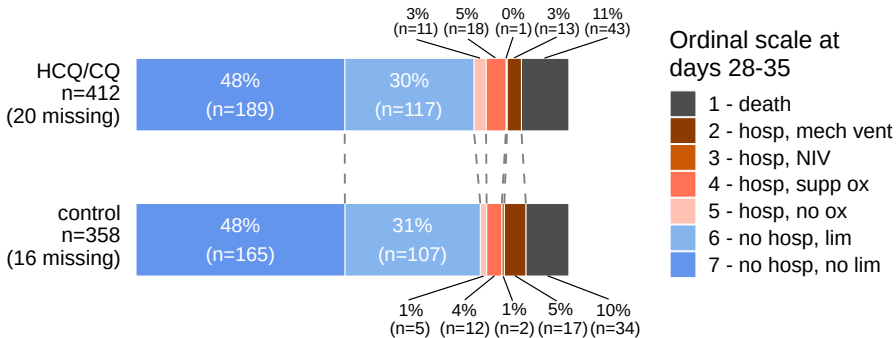
Panel A shows estimated proportional odds ratios comparing day 28-35 ordinal scale in HCQ/CQ versus control groups. Panel B shows estimated risk differences for day 28-35 mortality in HCQ/CQ versus control groups. Estimates are given for the pooled patient population and for subgroups. Blue circles represent model-standardized estimates; blue horizontal lines represent 95% credible intervals. Open grey circles represent plug-in estimates; grey horizontal lines represent 95% confidence intervals. Grey circle size represents the number of patients in the corresponding subgroup. Arrows indicate uncertainty intervals extending beyond plot limits.

Two of the trials did not have study acronyms (only trial registration numbers). Study acronyms are explained in the first footnote to Figure 1. 95% CrI indicates 95% credible intervals; HCQ/CQ, hydroxychloroquine or chloroquine; NA, not applicable; NIV, noninvasive ventilation (includes BiPAP/CPAP and/or high-flow oxygen); and OR, odds ratio.

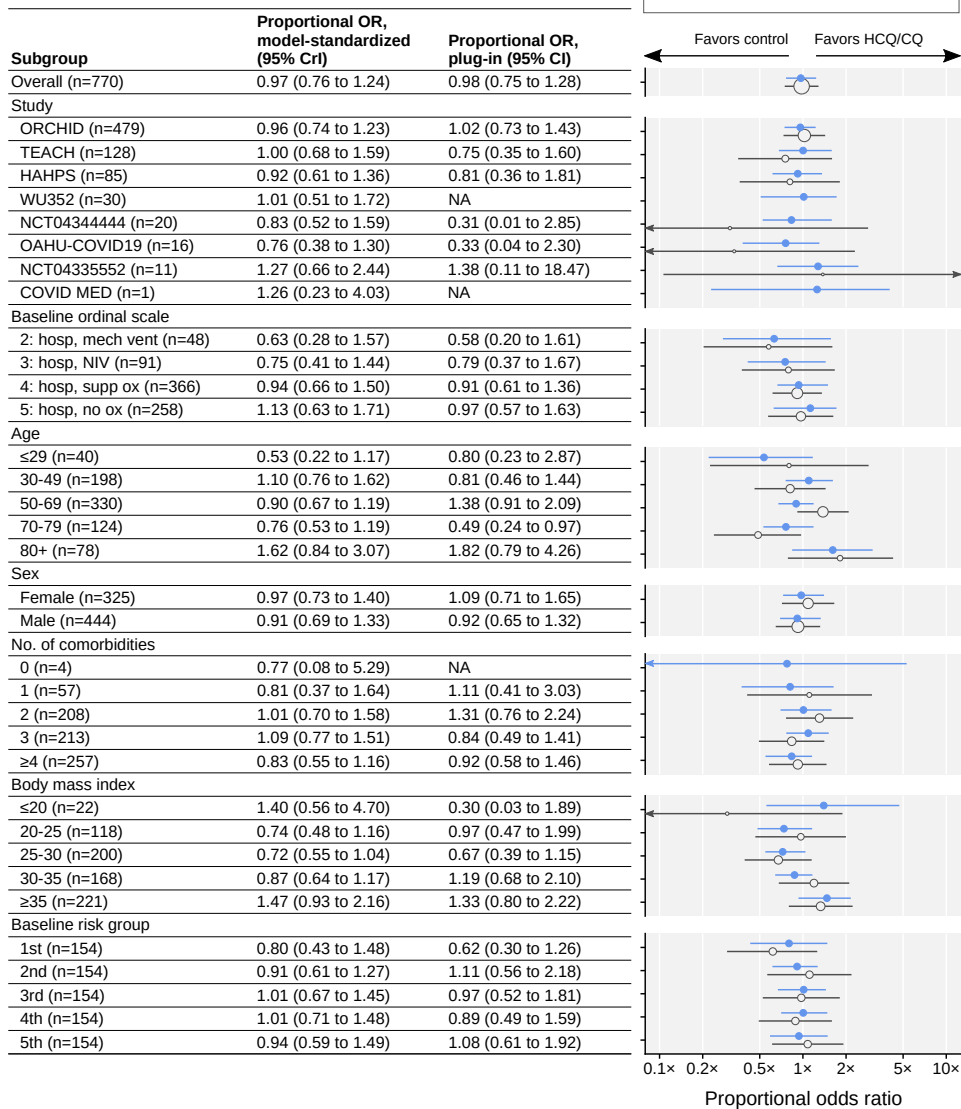
Figure 1. Trial Selection Process



^aTwo of the trials did not have study acronyms (only trial registration numbers). COVID MED indicates Comparison Of Therapeutics for Hospitalized Patients Infected With SARS-CoV-2 In a Pragmatic Adaptive randomizED Clinical Trial During the COVID-19 Pandemic; HAHPS, Hydroxychloroquine vs. Azithromycin for Hospitalized Patients With Suspected or Confirmed COVID-19; OAHU-COVID19, A Randomized, Controlled Clinical Trial of the Safety and Efficacy of Hydroxychloroquine for the Treatment of COVID-19 in Hospitalized Patients; ORCHID, Outcomes Related to COVID-19 Treated With Hydroxychloroquine Among In-patients With Symptomatic Disease; TEACH, Treating COVID-19 With Hydroxychloroquine; WU352, Washington University 352: Open-label, Randomized Controlled Trial of Hydroxychloroquine Alone or Hydroxychloroquine Plus Azithromycin or Chloroquine Alone or Chloroquine Plus Azithromycin in the Treatment of SARS CoV-2 Infection.



A Ordinal scale at days 28-35



B Mortality at days 28-35

Subgroup	Risk difference, model-standardized (95% CrI)	Risk difference, plug-in (95% CI)
Overall (n=770)	-0.01 (-0.04 to 0.02)	-0.01 (-0.06 to 0.04)
Study		
ORCHID (n=479)	-0.01 (-0.04 to 0.02)	0.00 (-0.05 to 0.06)
TEACH (n=128)	0.00 (-0.04 to 0.05)	-0.01 (-0.16 to 0.14)
HAHPS (n=85)	-0.03 (-0.07 to 0.05)	-0.12 (-0.26 to 0.02)
WU352 (n=30)	0.00 (-0.02 to 0.03)	NA
NCT04344444 (n=20)	-0.02 (-0.07 to 0.04)	0.13 (-0.37 to 0.64)
OAHU-COVID19 (n=16)	-0.04 (-0.12 to 0.02)	-0.20 (-0.58 to 0.18)
NCT04335552 (n=11)	0.01 (-0.03 to 0.08)	-0.08 (-0.73 to 0.57)
COVID MED (n=1)	0.01 (-0.16 to 0.09)	NA
Baseline ordinal scale		
2: hosp, mech vent (n=48)	-0.11 (-0.29 to 0.08)	-0.19 (-0.49 to 0.10)
3: hosp, NIV (n=91)	-0.06 (-0.19 to 0.08)	-0.11 (-0.32 to 0.09)
4: hosp, supp ox (n=366)	0.00 (-0.03 to 0.03)	0.00 (-0.06 to 0.05)
5: hosp, no ox (n=258)	0.01 (-0.01 to 0.04)	0.04 (-0.03 to 0.11)
Age		
≤29 (n=40)	-0.03 (-0.09 to 0.01)	-0.06 (-0.22 to 0.11)
30-49 (n=198)	0.00 (-0.02 to 0.03)	0.00 (0.00 to 0.00)
50-69 (n=330)	-0.02 (-0.05 to 0.01)	0.01 (-0.07 to 0.08)
70-79 (n=124)	-0.05 (-0.10 to 0.02)	-0.13 (-0.27 to 0.02)
80+ (n=78)	0.06 (-0.03 to 0.15)	0.17 (-0.07 to 0.41)
Sex		
Female (n=325)	-0.01 (-0.04 to 0.03)	0.01 (-0.06 to 0.08)
Male (n=444)	-0.01 (-0.05 to 0.03)	-0.02 (-0.08 to 0.04)
No. of comorbidities		
0 (n=4)	-0.03 (-0.26 to 0.27)	0.00 (0.00 to 0.00)
1 (n=57)	-0.04 (-0.09 to 0.04)	-0.08 (-0.22 to 0.06)
2 (n=208)	-0.01 (-0.04 to 0.03)	-0.03 (-0.10 to 0.04)
3 (n=213)	0.00 (-0.03 to 0.04)	0.04 (-0.05 to 0.12)
≥4 (n=257)	-0.03 (-0.08 to 0.03)	0.00 (-0.10 to 0.10)
Body mass index		
≤20 (n=22)	0.04 (-0.04 to 0.17)	-0.15 (-0.47 to 0.16)
20-25 (n=118)	-0.02 (-0.06 to 0.02)	0.01 (-0.12 to 0.14)
25-30 (n=200)	-0.04 (-0.09 to 0.00)	-0.05 (-0.16 to 0.05)
30-35 (n=168)	-0.03 (-0.06 to 0.01)	0.03 (-0.07 to 0.14)
≥35 (n=221)	0.03 (-0.01 to 0.06)	0.01 (-0.07 to 0.10)
Baseline risk group		
1st (n=154)	-0.01 (-0.02 to 0.01)	0.01 (-0.03 to 0.06)
2nd (n=154)	-0.01 (-0.02 to 0.01)	0.02 (-0.05 to 0.08)
3rd (n=154)	0.00 (-0.02 to 0.02)	0.00 (-0.06 to 0.07)
4th (n=154)	-0.01 (-0.05 to 0.03)	-0.05 (-0.17 to 0.07)
5th (n=154)	-0.03 (-0.15 to 0.07)	-0.03 (-0.19 to 0.13)

