Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19: an international collaborative meta-analysis of randomized trials

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Abstract

Background: Substantial COVID-19 research investment has been allocated to randomized clinical trials (RCTs) on hydroxychloroquine/chloroquine, which currently face recruitment challenges or early discontinuation. We aimed to estimate the effects of hydroxychloroquine and chloroquine on survival in COVID-19 from all currently available RCT evidence, published and unpublished.

Methods: Rapid meta-analysis of ongoing, completed, or discontinued RCTs on hydroxychloroquine or chloroquine treatment for any COVID-19 patients (protocol: https://osf.io/QESV4/). We systematically identified published and unpublished RCTs by September 14, 2020 (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, PubMed, Cochrane COVID-19 registry). All-cause mortality was extracted (publications/preprints) or requested from investigators and combined in random-effects meta-analyses, calculating odds ratios (ORs) with 95% confidence intervals (CIs), separately for hydroxychloroquine/chloroquine. Prespecified subgroup analyses included patient setting, diagnostic confirmation, control type, and publication status.

Results: Sixty-two trials were potentially eligible. We included 16 unpublished trials (1596 patients) and 10 publications/preprints (6317 patients). The combined summary OR on all-cause mortality for hydroxychloroquine was 1.08 (95%CI: 0.99, 1.18; I^2=0%; 24 trials; 7659 patients) and for chloroquine 1.77 (95%CI: 0.15, 21.13, I^2=0%; 4 trials; 307 patients). We identified no subgroup effects.

Conclusions: We found no benefit of hydroxychloroquine or chloroquine on the survival of COVID-19 patients. For hydroxychloroquine, the confidence interval is compatible with increased mortality (OR 1.18) or negligibly reduced mortality (OR 0.99). Findings have unclear generalizability to outpatients, children, pregnant women, and people with comorbidities.

Keywords: Meta-analysis, SARS-CoV-2, COVID-19, Hydroxychloroquine, Chloroquine

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has the potential of progression into respiratory failure and death.[1] More than 900,000 persons with COVID-19 globally have died by September, 2020,[2] and treatment options are limited.[3] The COVID-19 pandemic has caused a hitherto unprecedented search for possible therapies, with almost 700 clinical trials initiated in the first quarter of 2020 - and one in five of these trials target hydroxychloroquine (HCQ) or chloroquine (CQ) (unpublished data). This remarkable attention was primarily due to *in vitro* data,[4] immunomodulatory capacities,[5] and the oral formulation and well-documented safety profiles. In March 2020, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization of HCQ[6] and its prescription and usage outside clinical studies skyrocketed.[7] In many countries, HCQ or CQ were listed in treatment guidelines for COVID-19 (including, e.g., China, Ireland, and the US).[8] In a New York City cohort of 1376 COVID-19 inpatients during March-April 2020, 59% received HCQ.[9] However, the FDA revoked the Emergency Use Authorization on June 15, 2020.[10] At that point, two large randomized clinical trials (RCTs), RECOVERY and the WHO Solidarity trial, had stopped enrollment to their HCQ treatment arms.[11,12] An interim analysis of the RECOVERY trial showed no mortality benefit of HCQ.[12] Established as treatments of malaria and rheumatic disorders, HCQ and CQ may carry potentially severe adverse effects, especially related to cardiac arrhythmia.[5] Public uncertainty still remains, as illustrated by recent reports of planned use in pandemic epicenters in Central and South America.[13]

While many trials are ongoing, additional published evidence of potential benefits or harms may be several months away, if they even reach completion. Given the lack of favorable results in the large RECOVERY trial and the revoked Emergency Use Authorization, recruitment into HCQ and CQ trials has become increasingly difficult and many trials may run the risk of ending in futility. A rapid examination of data on all-cause mortality from as many trials as possible may offer the best evidence on potential survival benefits and to ensure that patients are not exposed to unnecessary risks if benefit is lacking. We used the infrastructure established with COVID-evidence,[14] a comprehensive database of COVID-19 trials funded by the Swiss National Science Foundation, to invite all

investigators of HCQ or CQ trials to participate in an international collaborative meta-analysis. We aimed to identify and combine all RCTs investigating the effects of HCQ or CQ on all-cause mortality in patients with COVID-19 compared to any control arm similar to the experimental arm in all aspects except the administration of HCQ or CQ.

Methods

This collaborative meta-analysis, registered before data collection,[15] focused solely on all-cause mortality in order to provide rapid evidence on the most critical clinical outcome. Investigators of ongoing, discontinued or completed trials were contacted via email to provide group-level (aggregated) mortality data per trial arm at any time point available.

We considered all clinical trials that reported randomly allocating patients with confirmed or suspected SARS-CoV-2 infection to a treatment protocol containing HCQ or CQ (for any duration or dose) or the same treatment protocol not containing HCQ or CQ. In other words, the control group had to receive placebo or no treatment other than standard of care (we excluded comparisons of HCQ or CQ against an active treatment, e.g., HCQ versus azithromycin, since active controls were too heterogeneous to pool together and reveal the pure benefits and harms of HCQ or CQ). Eligible ongoing trials had to provide data on all-cause mortality and randomize the first patient before June 1, 2020 (time point selected arbitrarily as we did not expect trials launched later to recruit enough patients to provide relevant additional information). Trials published or posted as preprint were not restricted by date. Prevention trials were not included. We included trials regardless of whether mortality was a primary outcome or not and put no restrictions on trial status, language, geographical region, or healthcare setting.

We searched for eligible trials registered at ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform [ICTRP] by June 11, 2020 (COVID-evidence database).[16] We additionally searched PubMed and the Cochrane COVID-19 trial registry (covering preprints, trial registries and literature databases) by June 11, 2020, using terms related to HCQ and CQ combined with terms for

COVID-19 and a standard RCT filter (Supplement 1).[17] We updated the literature search on September 14, 2020. Two authors (CA and AMS) independently verified the eligibility criteria (Figure 1) and solved any discrepancies by discussion.

Principal investigators of 83 potentially eligible trials were asked to confirm the eligibility criteria, as well as: "For each of your study arms: (a) What intervention did this group receive? (b) How many patients were randomized to this group? (c) Of these patients, how many have died? (d) Of these patients, for how many it is unknown if they are dead or alive?" (Supplement 2, email template). Investigators who were not responsive received two email reminders in English or Chinese, depending on trial origin.

The following information was extracted from all included RCTs by two reviewers (CA, AMS) and verified by the trial investigators: experimental and control arms, number of randomized participants, treatment schedule, patient setting, eligibility criteria, study location, blinding, target sample size, and trial status. We also classified trials as published in a peer-reviewed journal, posted on a preprint server, or unpublished (the latter category not including preprints). For reasons of feasibility within this rapid assessment, we generally did not request descriptive information beyond items included in trial registrations.

The main analysis evaluated separately the effect on all-cause mortality of HCQ versus control and CQ versus control. We report absolute numbers and proportions, as well as the treatment effect estimate as an odds ratio (OR; odds of death in the HCQ or CQ intervention group divided by the odds of death in the control group) with 95% confidence intervals (CIs). For multi-arm studies, we requested data for all arms and calculated treatment effect estimates for each eligible comparison. We combined mortality effects from all RCTs based on binary outcome data (2x2 contingency tables) in meta-analyses and describe the statistical heterogeneity using the I^2-statistic.[18] In our protocol, we prespecified a random-effects model of the Hartung-Knapp-Sidik-Jonkman (HKSJ) approach,[19] in order to provide more equality of weights between trials with moderate to large size (than for example the DerSimonian-Laird approach). We did not prespecify the between-study variance estimator, tau-

squared, but chose the Paule and Mandel (PM) estimator based on provided guidance on choosing among 16 variants.[20] Cases of zero events in one arm were corrected by adding the reciprocal of the size of the contrasting study arm.[17] However, considering the range of sample sizes and numbers of zero events across trials, we assessed the effects of alternative approaches with sensitivity analyses, as detailed below. To explore and illustrate evidence generation over time, we also performed a cumulative meta-analysis of all trials as well as stratified by dissemination status (publications/preprints vs unpublished), using the HKSJ approach with PM tau-squared. We used the date of email response or publication/posting of preprint. The meta-analyses were completed using R version 3.5.1 and the 'meta' package version 4.13-0.

We stratified trials by patient setting (as proxy to COVID-19 severity: outpatients, inpatients but not intensive care unit (ICU), and ICU), diagnostic confirmation (confirmed SARS-CoV-2 versus suspected cases), control type (placebo control versus other) and publications/preprints versus unpublished trials. We did not stratify for missing data since the amount was extremely low. A post-hoc stratification by HCQ dose was added (trials with ≥1600 mg on day 1 and ≥800 mg from day 2 versus lower-dose trials) to isolate trials predicted to achieve blood levels of HCQ above the *in vitro* half maximal inhibitory concentration (IC50) value for SARS-CoV-2 (1.13 μM).[21]

We added exploratory sensitivity analyses to assess robustness across meta-analytic approaches: DerSimonian-Laird and Sidik-Jonkman tau-squared estimators, Mantel-Haenszel random-effects method, and Peto method. DerSimonian-Laird is a standard random-effects meta-analysis approach, but may underestimate uncertainty. The Sidik-Jonkman tau-squared estimator, on the other hand, may yield inflated estimates if heterogeneity is low.[20] The Mantel-Haenszel method performs reasonably well with small and zero event counts, much like Peto and arcsine transformation. The Peto method is suboptimal in the presence of substantial imbalances in the allocation ratio of patients randomized in the compared arms (e.g., RECOVERY trial). We also modeled variants to handling zero events (arcsine difference, and excluding trials with zero events) as well as excluding trials with <50 participants.

Results

Our search identified 146 randomized trials investigating HCQ or CQ as treatment for COVID-19, of which 83 were deemed potentially eligible after scrutinizing the randomized comparisons. The investigators of these 83 trials were contacted and 57% (47 of 83) responded (Figure 1). Of the responders, 19 trials were eligible and available (16 unpublished and three preprints); 21 trials were ineligible according to information provided; five responding investigator teams were not ready to share their results yet; and two declined participation. For the 36 trials without response, five were confirmed eligible and available (three publications and two preprints); two were confirmed ineligible; and for the remaining 29, results were not available, nor could they be confirmed eligible. Individual trial characteristics are presented in Table 1 (26 included trials) and Supplement Table S1 (36 potentially eligible but unavailable). Overall, trial characteristics were not different between included and unavailable trials (Table 2).

We included 26 trials (Table 1; 16 unpublished trials, five publications, and five preprints; of these, one publication and one preprint were identified in our search update).[12,22–30] HCQ was evaluated in 24 trials (7659 patients), and CQ was evaluated in four trials (307 patients). Two trials investigated both HCQ versus control and CQ versus control (63 patients). The median sample size was 58 (IQR 24 to 207) for HCQ trials and 42 (IQR 35 to 234) for CQ trials. One very large trial (RECOVERY) included 62% of all patients in the HCQ trials. Most trials investigated HCQ or CQ in hospitalized patients (20 trials; 77%), and only five trials (19%) had an outpatient setting. The average mortality was 10% (standard deviation 13%) in inpatient trials and 0.08% (standard deviation 0.18%) in outpatient trials. The comparator was in eleven trials placebo (42%) and in 14 (54%) no other treatment than standard of care. In most trials, patients and clinicians were aware of the treatment (13 trials; 50%), while in one trial (4%) the patients were blinded and in eleven trials (42%) patients and clinicians were blinded (Table 2).

Regarding HCQ, in the 24 included trials, 499 of 3020 (16.5%) patients treated with HCQ died and 874 of 4639 patients (18.8%) in the control groups died. In the meta-analysis, the combined OR was 1.08 (95% CI, 0.99 to 1.18, p = 0.07), with low heterogeneity (I^2 = 0%) (Figure 2A). In 11 trials including a total of 782 patients, there were zero deaths in both arms.

Regarding CQ, in the 4 included trials, 18 of 160 (11%) patients treated with CQ died and 12 of 147 patients (8%) in the control groups died. The combined OR was 1.77 (95% CI: 0.15 to 21.13, p = 0.21), with low heterogeneity (I^2 = 0%) (Figure 2B). In two of four trials including a total of 217 patients, there were zero deaths in both arms.

The available evidence in this study is the result of publications, preprints or personal communication accrued over four months (from April 10, 2020 to August 12, 2020), with on average one trial added every fifth day (Figure 3A-C).

Results for the effects of HCQ on mortality were quite similar across subgroups (Supplement Table S2A). When only including published information (publications and preprints, excluding unpublished trials), there was a statistically significant harmful effect of HCQ (OR 1.10, 95% CI 1.07 to 1.13), while among the unpublished trials there was no such conclusion of harm (OR 0.96, 95% CI 0.71 to1.30, *p* for interaction = 0.320). We conducted no subgroup analyses for CQ, as there were only two trials with events. In the sensitivity analyses employing different meta-analytical approaches (Supplement Table S2B and Figures S1A-C), results were consistent.

Discussion

This collaborative meta-analysis of 26 published or unpublished RCTs, including 7966 patients, found no overall survival benefit of HCQ or CQ as treatment options for COVID-19 patients. No differences were seen across subgroup analyses on patient setting, diagnosis confirmation, control type, publication status or dose. For CQ, the number of studies was too small to draw clear conclusions.

This meta-analysis offers useful insights for a challenging health situation. Hundreds of thousands of patients have received HCQ and CQ outside of clinical trials without evidence of their beneficial effects. Public interest is unprecedented, with weak early evidence supporting HCQ's merits being widely discussed in some media and social networks - despite the unfavorable results by a very large RCT. Numerous clinical studies have been investigating HCQ and CQ almost simultaneously. Although seven systematic reviews and meta-analyses are already available, they only consider the small handful of RCTs being already published (which were all included here).[31–35] While data sharing has been rather limited to-date in biomedical research, such openness can be transformative in generating knowledge. This pandemic has brought together a collaboration of clinical trialists agreeing to share their data, which allows this study to not only summarize the existing evidence, but also illustrate the accumulation of evidence that would otherwise not be available.

For HCQ, evidence is dominated by the RECOVERY trial,[12] which indicated no mortality benefit for treated COVID-19 patients, together with longer hospitalization and higher risk of progression to invasive mechanical ventilation and/or death. Adding the few other available publications or preprints, one would have concluded a statistically significant increased mortality in COVID-19 patients treated with HCQ. Considering also the unpublished data, which tend towards a null effect, this meta-analysis' confidence intervals are compatible with increased mortality (OR 1.18) or negligibly reduced mortality (OR 0.99). The tendency of published trials to report larger effect sizes than unpublished trials is well-documented and constitute one of the reporting biases that are discernable only when a body of studies are considered together.[36] Null results are less expected to be

rapidly disseminated, especially if the trial is small. Of note, RECOVERY results showing dexamethasone benefits have been published more rapidly [3] than the unfavorable HCQ results.[12] This paper offers the most comprehensive summary on HCQ and mortality in COVID-19 to date.

This meta-analysis does not address prophylactic use nor other outcomes besides mortality. Also, generalizability is unclear for certain populations. All but three trials excluded children and the majority excluded pregnant or breastfeeding women. Among five studies on outpatients, there were three deaths, two occurring in the one trial of 491 relatively young patients with few comorbidities,[24] and one occurring in a small trial with 27 patients. For outpatients that are elderly or have comorbidities, evidence is sparse. Most of the 26 trials excluded persons with comorbid conditions carrying higher risk of adverse events from HCQ/CQ.[22–24] No evidence is in the pipeline for these groups, which echoes clinical reasoning being reluctant to expose them to risk.

Twenty percent of the potentially eligible trials were listed as discontinued, mostly because of fewer patients than expected. Among 26 included RCTs, only two had reached their target sample size at the time of censoring for this meta-analysis. As previously discussed,[4] most trials on HCQ and CQ in COVID-19 are small, reflecting both the strong motivation for individual efforts and underscoring the need for readily available research infrastructure to merge small-scale initiatives (unpublished data). Especially in the context of recruitment challenges, we encourage other researchers to form collaborations and combine trial results.[37]

Our analysis has some limitations. First, although we adopted a comprehensive, systematic search strategy, our real-time initiative differs from traditional systematic reviews. We focused on collecting unpublished information, aiming to rapidly secure as much trial evidence as possible. We did not review individual trials, nor break down results according to patient characteristics. Such analyses are planned in future publications using in-depth details disclosed in individual trial publications to come.[38–40] However, consistent findings in placebo-controlled, double-blinded and open-label trials indicate an overall low risk of bias across trials; moreover, attrition was negligible (median 0%, IQR

0% to 0%; range 0 to19.5%). Meta-epidemiological work shows that mortality results are least affected by lack of blinding, or problems in randomization and allocation concealment as compared with other outcomes.[41] Second, a majority of the potentially eligible trials were not available. Despite going far beyond the standard review of published evidence, we expect additional results from future trials to narrow the uncertainty of the treatment effect and possibly reveal benefits or harms not discernible based on the current evidence. Of the unavailable trials, the WHO Solidarity trial may have the largest sample size and provide most mortality data. We plan to perform an update when substantial additional evidence becomes available. Finally, although conclusions were robust across sensitivity analyses addressing model specifications, one combination (HKSJ model with SJ tau-squared estimator) yielded substantially wider confidence intervals. This combination gave disproportionately low weight to RECOVERY (16%) and we consider the main model (HKSJ with PM tau-squared estimator) to be more valid in this situation.

Treatment with HCQ or CQ for COVID-19 showed no survival benefit based on currently available data. Medical professionals around the globe are encouraged to inform patients that HCQ should not be looked upon as a cure of COVID-19. Physicians who choose to prescribe HCQ for COVID-19 do so with very sparse evidence and need to consider the risk they are exposing their patients to without known concomitant benefit. Additional trials may solidify or modify the current picture of the evidence on these treatment options.

Declarations

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

Benjamin Abella and Ravi Amaravadi are the primary investigators of the Prevention and Treatment of COVID19 with Hydroxychloroquine (PATCH) trial, funded by a philanthropic gift. Ravi Amaravadi reports being founder with equity of Pinpoint Therapeutics and Immunacell, and personal fees from Sprint Biosciences and Deciphera, outside the submitted work. Derek Angus reports personal fees from Ferring Pharmaceuticals, Inc., Bristol-Myers Squibb, and Bayer AG, other from Alung Technologies, Inc., outside the submitted work; in addition, Dr. Angus has pending patents for Selepressin - compounds, compositions and methods for treating sepsis to Ferring, B.V., and Proteomic biomarkers of sepsis in elderly patients pending to University of Pittsburgh. Yaseen Arabi reports that he is principal investigator on a clinical trial of lopinavir–ritonavir and interferon for Middle East respiratory syndrome (MERS) and that he was a non-paid consultant on therapeutics for MERS-coronavirus (CoV) for Gilead Sciences and SAB Biotherapeutics. He is a co-investigator on the Randomized, Embedded, Multi-factorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), a board member of the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), and the Lead-Co Chair of the Think20 (T20) Taskforce for COVID-19. Brigham and Women's Hospital, PRA Health Science, and Cliniques universitaires Saint-Luc received funds from Sanofi. Thomas Benfield reports grants from Pfizer, Novo Nordisk Foundation, Simonsen Foundation, Lundbeck Foundation, and Kai Hansen Foundation; grants and personal fees from GSK, Pfizer, Boehringer Ingelheim, and Gilead; and personal fees from MSD, all outside the submitted work. Yehuda Cohen, Lisa Cowan, Bruno Igau, and Laurent Perrin are employees of Sanofi. The COV-HCQ and COMIHY trials were supported by the German Federal Ministry of Education and Research (EudraCT number 2020-001224-33) and the German Federal

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None of the other authors have any competing interests to declare.

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Authors' contributions

Lars G. Hemkens, Cathrine Axfors and Andreas M. Schmitt had full access to all data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Lars G. Hemkens, John P. A. Ioannidis, Cathrine Axfors, Andreas M. Schmitt, Steven N. Goodman, David Moher

Acquisition, analysis, or interpretation of data: All authors

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Tables

Table 1. Group-level characteristics of randomized clinical trials evaluating hydroxychloroquine or chloroquine as treatment for COVID-19.

Acronym	Register ID	Treatment comparison		Treatment schedule	Setting	Age	Mortality (%)	Location	Blinding	Targeted sample size	Status
		Experimental arm (n)	Control arm(n)								
Published*											
-	ChiCTR2000029559	HCQ (31)	No Treatment (31)	200 mg twice a day for 5 days	Inpatient	≥18 years	0	China	Participant, Caregiver	300	Completed
-	ChiCTR2000029868	HCQ (75)	No Treatment (75)	1200 mg/day for 3 days, then 800 mg/day for 11-18 days	Inpatient	≥18 years	0	China	None	360	Completed
-	NCT04261517	HCQ (15)	No Treatment (15)	400 mg/day for 5 days	Inpatient	≥18 years	0	China	None	30	Completed
RECOVERY	NCT04381936	HCQ (1561)	No Treatment (3155)	800 mg at zero hours, then 800 mg after 6 hours, then 800 mg/day for up to 9 days	Inpatient	≥18 years	25.57	United Kingdom	None	12000*	Completed **
-	ChiCTR2000030054	HCQ (18)	No Treatment (12)	400 mg/day for 10 days	Inpatient	18 to 75 years	0	China	None	100	Completed
		CQ (18)	No Treatment (12)	1000 mg/day for 1 day, then 500 mg/days for 9 days			0				
NO COVID-19	NCT04316377	HCQ (27)	No Treatment (26)	800 mg/day for 7 days	Inpatient	≥18 years	3.77	Norway	None	202	Halted
-	NCT04384380	HCQ (21)	No Treatment (12)	800 mg/day for 1 day, then 400 mg/day for 6 days	Inpatient	20 to 79 years	0	Taiwan	None	45	Recruiting
COVID-PEP	NCT04308668	HCQ (244)	Placebo (247)	800 mg at zero hours, then 600 mg after 6-8 hours, then 600 mg daily for 4 days	Outpatient	≥18 years	0.41	International ***	Participant, Caregiver	3000	Completed
BCN PEP CoV-2	NCT04304053	HCQ (136)	No Treatment (157)	800mg on day 1, and 400mg/day on days 2-7	Outpatient	≥18 years	0	Spain	None	2300	Completed
Coalition I	NCT04322123	HCQ (221)	No Treatment (227)	800 mg/day for 7 days	Inpatient	≥18 years	2.90	Brazil	None	630*	Halted

Unpublished*											
PATCH	NCT04329923	HCQ (15)	Placebo (15)	800 mg/day for up to 14 days	Inpatient	≥40 years	0	United States	Participant, Caregiver	400*	Recruiting
CCAP-1	NCT04345289	HCQ (1)	Placebo (1)	600 mg/day for 7 days	Inpatient	≥18 years	0	Denmark	Participant, Caregiver	1500*	Discont.
-	NCT04335552	HCQ (4)	No Treatment (2)	800 mg/day for 1 day, then 600 mg/day for 4 days	Inpatient	≥12 years	16.67	United States	None	500	Discont.
		HCQ + Azithromycin (2)	Azithromycin (3)				60				
ARCHAIC	NL8490	CQ (5)	No Treatment (3)	600 mg at zero hours, then 300 mg after 12 hours, then 600 mg/day for 4 days	Inpatient	≥18 years	12.50	Netherlands	None	950	Discont.
		HCQ (4)	No Treatment (3)	800 mg/day for 1 day, then 400 mg/day for 4 days			28.57				
CloroCOVID19II	NCT04342650	CQ (78)	Placebo (74)	900 mg/day for 1 day, then 450 mg/day for 4 days	Outpatient	≥18 years	0	Brazil	Participant, Caregiver	210	Completed
	NCT04323527	CQ (41)	Placebo (41)	900 mg/day for 1 day, then 450 mg/day for 4 days	Inpatient	≥18 years	35.37	Brazil	Participant, Caregiver	278	Completed
HYDRA	NCT04315896	HCQ (75)	Placebo (77)	400 mg/day for 10 days	Inpatient	18 to 80 years	37.50	Mexico	Participant, Caregiver	500	Recruiting
-	ChiCTR2000031204	CQ (18)	Placebo (17)	1000 mg on day 1, then 500 mg/day on days 2-3, then 250 mg/day until ≤14 days of total treatment	Inpatient	18 to 70 years	0	China	Participant	300	Recruiting
-	NCT04333654	HCQ (5)	Placebo (3)	800 mg at zero hours, then 400 mg 6-8 hours later, then 600 mg/day for 9 days	Outpatient	18 to 80 years	0	International ***	Participant, Caregiver	210	Discontinued
-	NCT04353336	HCQ (97)	No Treatment (97)	800 mg/day on day 1, then 400 mg/day for 14 days	Inpatient	All	5.67	Egypt	None	40	Recruiting
PROTECT	NCT04338698	HCQ + Azithromycin + Oseltamivir (64)	Azithromycin + Oseltamivir (64)	600 mg/day for 5 days	Inpatient	≥18 years	0	Pakistan	Investigator	500	Recruiting
		HCQ + Oseltamivir (62)	Oseltamivir (63)				0.80				
		HCQ + Azithromycin (59)	Azithromycin (61)				2.50				

TEACH	NCT04369742	HCQ (67)	Placebo (61)	800 mg/day on day 1, then 400 mg/day for 4 days	Inpatient	All	10.16	United States	Participant, Caregiver	626	Discont.
OAHU-COVID19	NCT04345692	HCQ (10)	No Treatment (6)	800 mg/day on day 1, then 400 mg/day for 4 days	Inpatient	18 to 95 years	12.50	United States	None	350	Recruiting
REMAP-CAP	NCT02735707	HCQ (61)	No Treatment (81)	800 mg at zero and six hours, then 800 mg/day for up to 6 days	ICU	≥18 years	27.46	International ***	None	No fixed target sample	Completed **
-	NCT04325893	HCQ (124)	Placebo (123)	800 mg on day 1, then 400 mg/day for 8 days	Inpatient	≥18 years	6.88	France	Participant, Caregiver	1300	Recruiting
COV-HCQ	NCT04342221	HCQ (13)	Placebo (14)	800mg/day on day 1 and 600 mg/day for days 2-7	Inpatient	≥18 years	3.70	Germany	Participant, Caregiver	220	Recruiting
COMIHY	NCT04340544	HCQ (8)	Placebo (8)	600mg/day for 7 days	Outpatient	≥18 years	0	Germany	Participant, Caregiver	2700	Recruiting

Abbreviations: chloroquine (CQ), hydroxychloroquine (HCQ)

* Trial includes more treatment arms than reported here; target sample size refers to all arms. ** Other arms of the trial are still ongoing. *** Including centers in multiple countries. **** Including peer-reviewed journal publications and posted preprints.

Table 2. Group-level characteristics of included and unavailable trials.

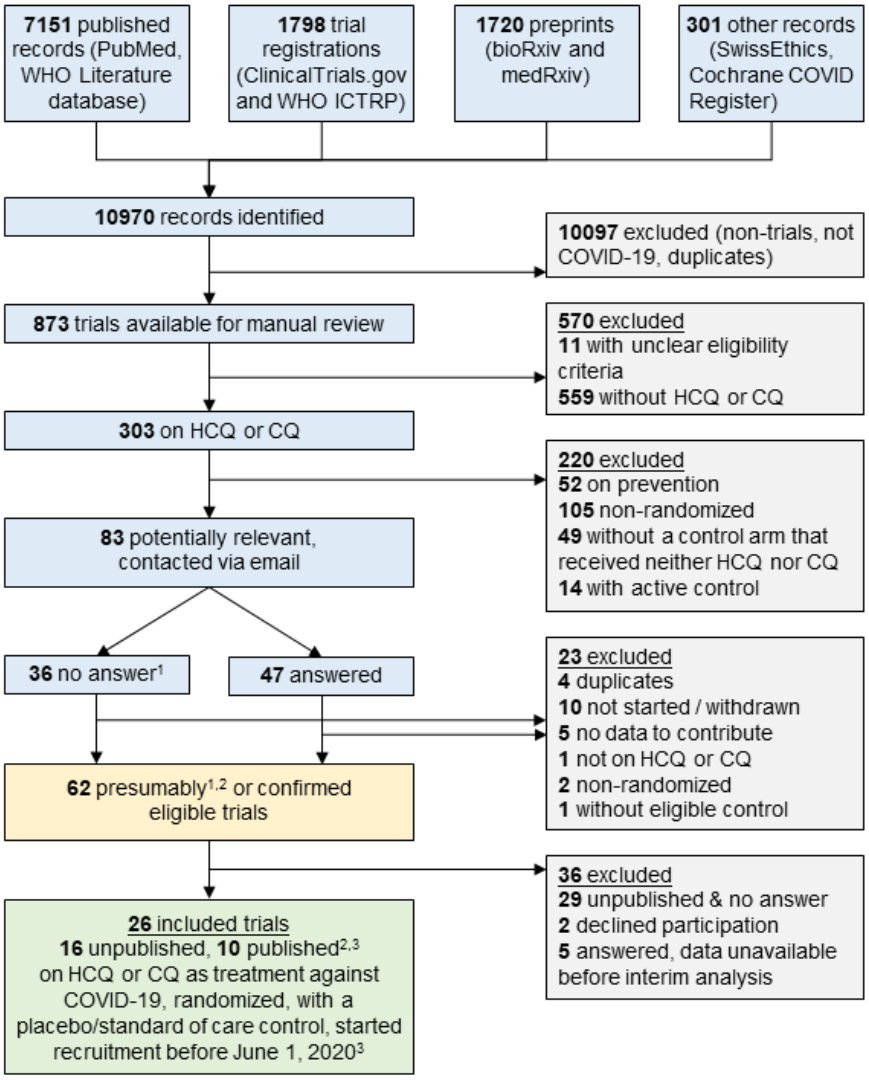
	All trials n = 62	Included trials n = 26	Potentially eligible, unavailable trials* n = 36
Drug, n (%)			
HCQ	47 (76)	22 (85)	25 (69)
CQ	10 (16)	2 (8)	8 (22)
Both	5 (8)	2 (8)	3 (8)
Planned sample size*, median (IQR)	355 (150 to 693)	450 (212 to 1212)	308 (120 to 540)
Trial status, n (%)			
Completed	9 (15)	8 (31)	1 (3)
Discontinued	14 (23)	5 (19)	9 (25)
Not yet recruiting	7 (11)	0	7 (19)
Recruiting	32 (52)	13 (50)	19 (53)
Location, n (%)			
Africa	3 (5)	1 (4)	2 (6)
Asia	22 (35)	7 (27)	15 (42)
Europe	17 (27)	8 (31)	9 (25)
International	5 (8)	2 (8)	3 (8)
North America	10 (16)	4 (15)	6 (17)
Oceania	1 (2)	1 (4)	0
South America	4 (6)	3 (12)	1 (3)
Placebo control, n (%)	30 (48)	11 (42)	19 (53)
More than two arms, n (%)	27 (44)	9 (36)	18 (50)
Patient setting, n (%)			
ICU	1 (2)	1 (4)	0
Inpatient	45 (73)	20 (77)	25 (69)
Outpatient	12 (19)	5 (19)	7 (19)
Unclear	4 (6)	0	4 (11)
Blinding, n (%)			
None	31 (50)	13 (50)	18 (50)
Outcome Assessor	1 (2)	1 (4)	0
Participant	3 (5)	1 (4)	2 (6)
Participant, Caregiver	26 (42)	11 (42)	15 (42)
Participant, Outcome Assessor	1 (2)	0	1 (3)

Abbreviations: chloroquine (CQ), hydroxychloroquine (HCQ), intensive care unit (ICU), interquartile range (IQR)

* Data were extracted from trial registries or publications. ** Including centers in multiple countries.

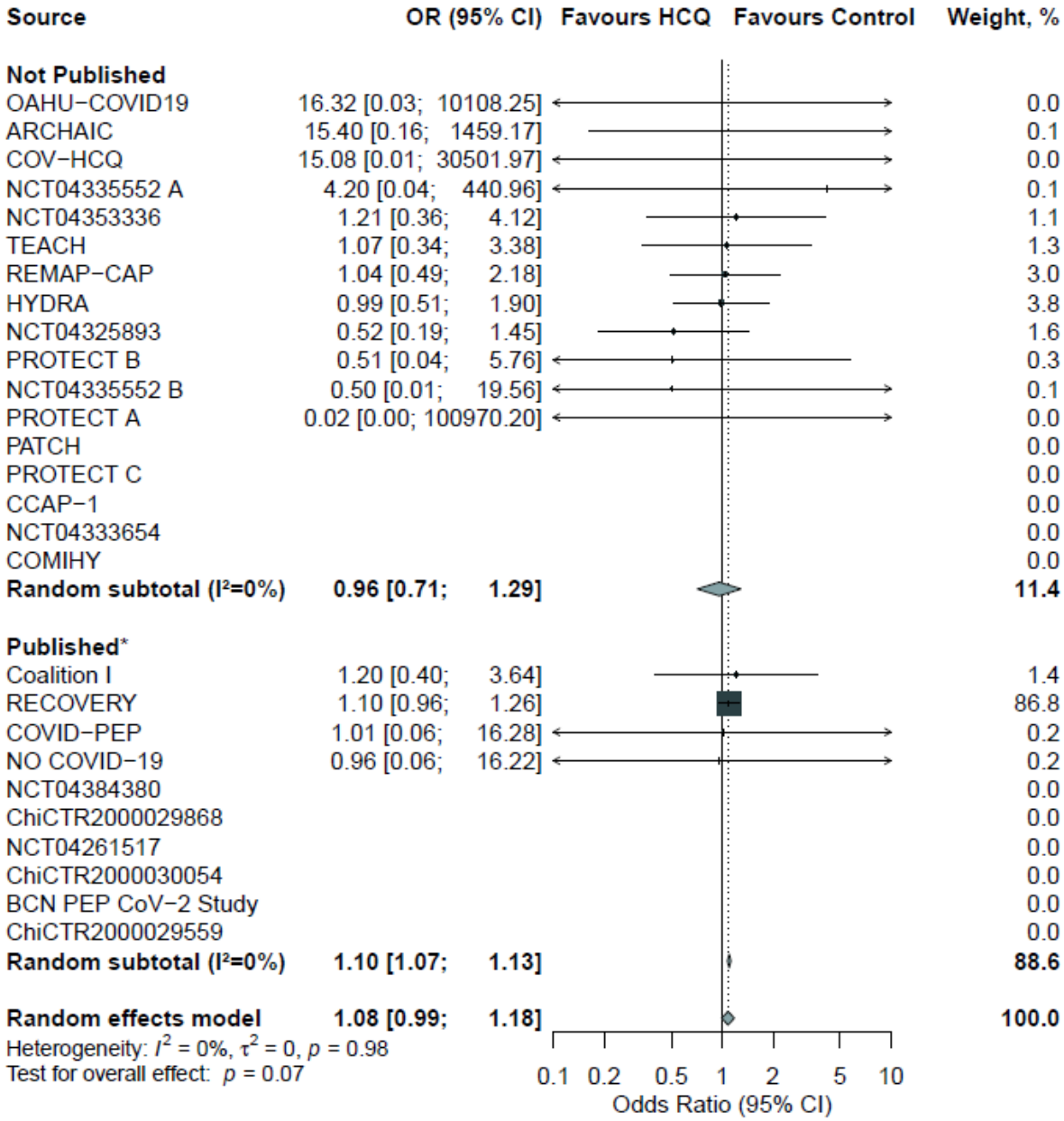
Figures

Figure 1. Flowchart of included randomized clinical trials.



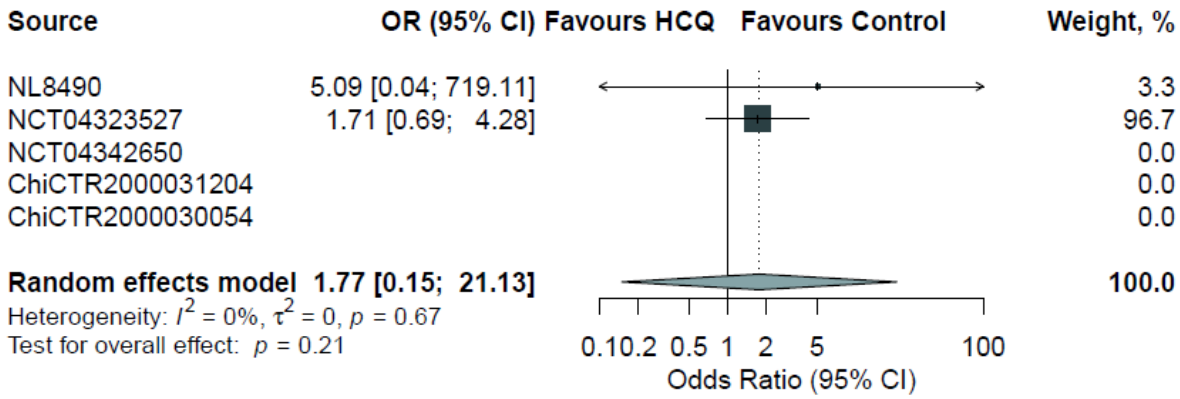
Sources searched up to June 11, 2020 (PubMed, ClinicalTrials.gov, WHO ICTRP, Cochrane COVID Register) or April 9 (WHO Literature database, bioRxiv, medRxiv, SwissEthics). [1] Trials for which we received no answer were presumed to be eligible unless withdrawn. [2] One publication and one preprint were identified in a later search update. [3] Published peer-reviewed articles or posted preprints. Abbreviations: chloroquine (CQ), hydroxychloroquine (HCQ), International Clinical Trials Registry Platform (ICTRP), World Health Organization (WHO).

Figure 2A. Random effects meta-analysis for mortality for treatment of COVID-19 with Hydroxychloroquine, trials are stratified by publication status.



* Published as peer-reviewed articles or posted preprints.

Figure 2B. Random effects meta-analysis for mortality for treatment of COVID-19 with Chloroquine.



The x-axis scales differ for reasons of readability.

Figure 3A. Cumulative meta-analysis for mortality for treatment of COVID-19 with Hydroxychloroquine.

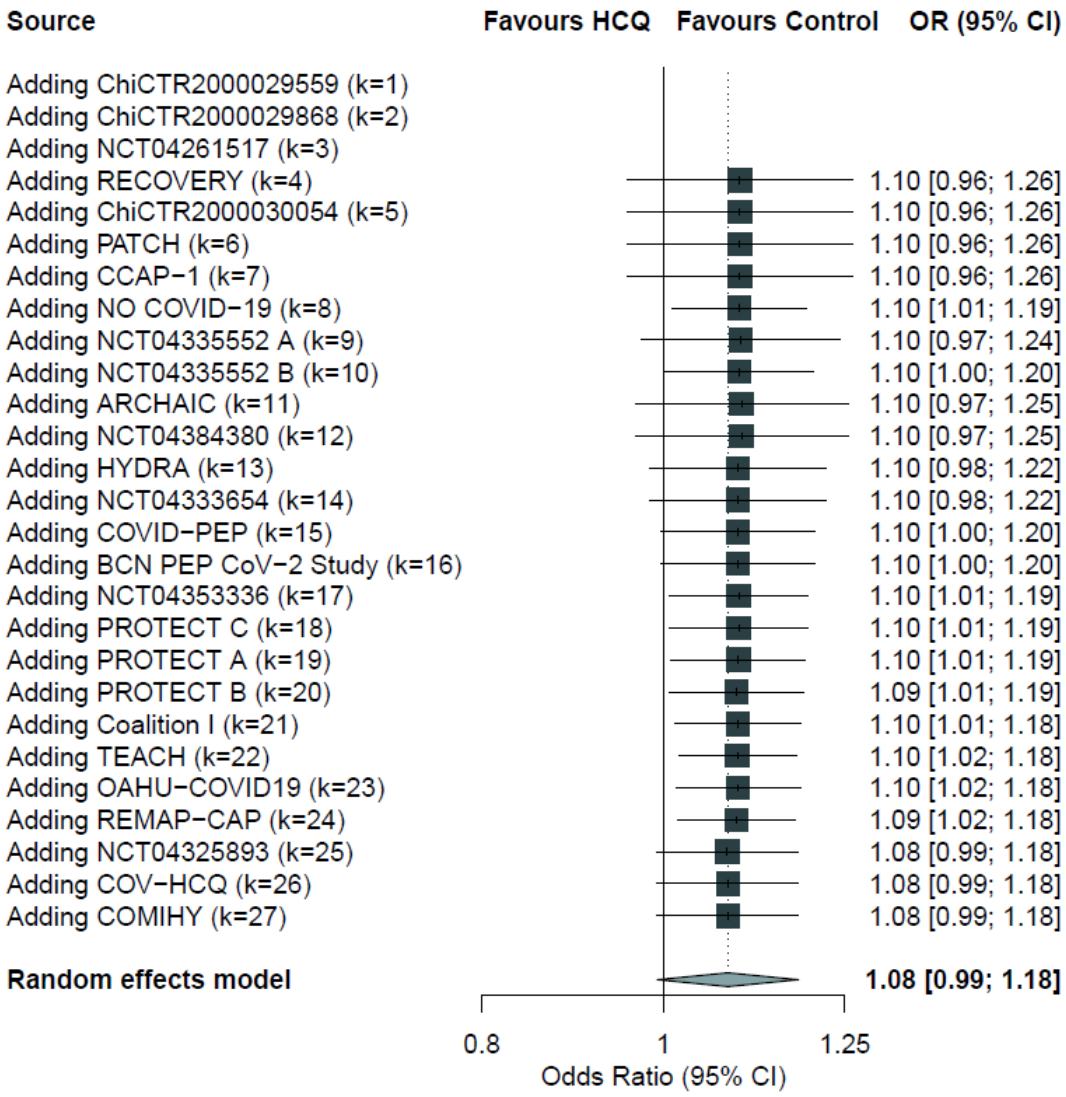


Figure 3B. Cumulative meta-analysis for mortality for treatment of COVID-19 with Hydroxychloroquine (publications and preprints only)

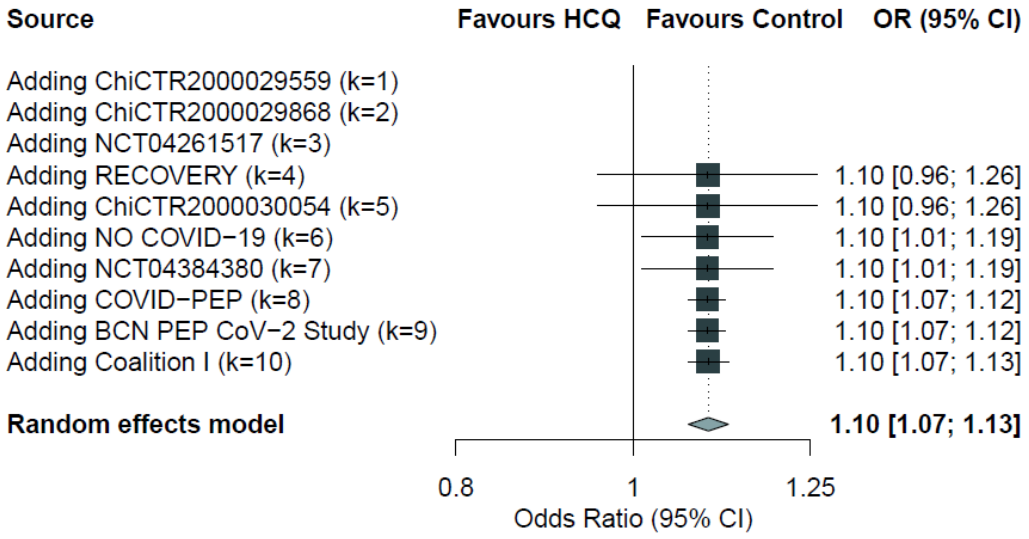
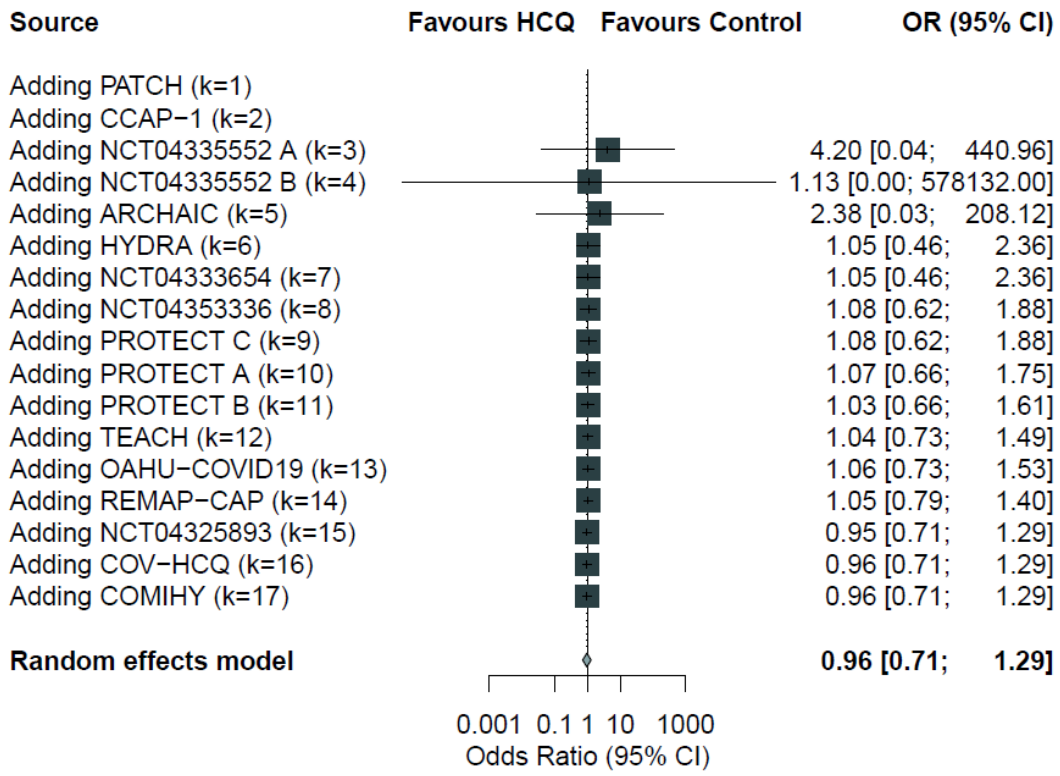


Figure 3C. Cumulative meta-analysis for mortality for treatment of COVID-19 with Hydroxychloroquine (unpublished data only)



The x-axis scales differ for reasons of readability.