A Rapid Systematic Review of Clinical Trials Utilizing Chloroquine and Hydroxychloroquine as a Treatment for COVID-19

MD Sadakat Chowdhury[1], Jay Rathod[1], Joel Gernsheimer, MD[2]

[1]SUNY Downstate Medical Center, [2]SUNY Downstate Medical Center Department of Emergency Medicine

Corresponding author: MD Sadakat Chowdhury, BS, SUNY Downstate Medical Center, 450 Clarkson, Avenue, Brooklyn, NY 11203, USA. Email: MDSadakat.Chowdhury@downstate.edu

Additional authors:

Jay Rathod, BS, SUNY Downstate Medical Center, 450 Clarkson, Avenue, Brooklyn, NY 11203, USA. Email: Jay.Rathod@downstate.edu

Joel Gernsheimer, MD, SUNY Downstate Medical Center Department of Emergency Medicine, 450 Clarkson, Avenue, Brooklyn, NY 11203, USA. Email: Joel.Gernsheimer@downstate.edu

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MR. MD SADAKAT CHOWDHURY (Orcid ID : 0000-0001-6268-512X)

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Abstract:

Background: The emergence of SARS-CoV-2 has presented clinicians with a difficult therapeutic dilemma. With supportive care as the current mainstay of treatment, the fatality rate of COVID-19 is 6.9%. There are currently several trials assessing the efficacy of different antivirals as treatment. Of these, Chloroquine (CQ) and derivative, Hydroxychloroquine (HCQ), have garnered the most attention.

Methods: In this study, the literature currently available on CQ and HCQ as treatment of COVID-19 was surveyed using EMBASE, PubMed, Cochrane Librar, MedRxiv and 1 clinical trial registry. Upon gathering published and preprint trials, risk of bias was assessed using Cochrane Risk of Bias Tool 2.0.

Results: There are currently 7 completed clinical trials and 29 registered clinical trials focusing on HCQ or CQ as a therapeutic avenue for COVID-19. Of these, 5/7 trials have shown favorable outcomes for patients using CQ or HCQ and 2/7 have shown no change compared to control. However, all 7 trials carried varying degrees of bias and poor study design.

Conclusion: There is currently not enough data available to support the routine use of HCQ and CQ as therapies for COVID-19. Pending further results from more extensive studies with more stringent study parameters, clinicians should defer from routine use of HCQ and CQ. There are several clinical trials currently underway with results expected soon.

Introduction

Coronaviruses are positive-sense, single-stranded enveloped RNA viruses. In December 2019, a novel coronavirus endemic to China was identified as the cause of a series of pneumonia cases in the region of Wuhan. The virus spread rapidly thereafter, resulting in the World Health Organization (WHO) declaring it a pandemic in March of 2020[1]. The novel coronavirus was named severe acute respiratory syndrome coronavirus (SARS-CoV-2), and the disease caused by the virus named COVID-19. Current theories suggest a zoonotic origin with genomic analysis showing a close resemblance with two other highly contagious human coronaviruses, MERS-CoV and SARS-CoV[2]. As of April 26th, 2020, there have been more than 2,900,000 cases reported globally, with more than 206,000 deaths and 860,000 recoveries from COVID-19, according to Johns Hopkins University[3].

Presently, the mainstay of treatment for COVID-19 thus far has been mainly supportive. Those with non-severe illnesses (fever, cough, myalgias, etc.) are managed with home care and self-isolation. Home care includes use of hydration, antipyretics, analgesics, and antitussives as necessary with use of face masks and the maintenance of 6 feet distance when in the presence of other people. Frequent handwashing and disinfection of frequently touched surfaces is also recommended by the CDC[4]. Those with illness proven by positive COVID-19 screening tests are advised to discontinue home isolation at least 7 days after start of symptoms, and at least 3 days after becoming asymptomatic (resolution of fever and respiratory symptoms). Those who are asymptomatic are asked to self-isolate for at least seven days after a positive test result.[5] The with severe COVID-19 are admitted into the hospital, where they are managed with oxygen support via high flow oxygen or noninvasive positive pressure ventilators. Currently, the WHO recommends against the use of glucocorticoids[6]. Some patients go on to develop acute respiratory distress syndrome (ARDS) requiring intubation with mechanical ventilation in an ICU setting. There has recently been investigation exploring the use of certain antivirals in the treatment of COVID-19, with clinical trials currently underway measuring their effectiveness. Some of these experimental treatments include Remdesivir, Chloroquine/Hydroxychloroquine, IL-6 inhibitors, convalescent plasma, Favipiravir, and Lopinavir-ritonavir. Of these, Chloroquine/Hydroxychloroquine has gained the most media attention after President Donald Trump of the United States urged patients to take it[7].

Chloroquine (CQ) is used extensively as an antimalarial and immunomodulating agent. Hydroxychloroquine (HCQ), a derivative of CQ with an extra hydroxyl group, is shown to be less toxic than CQ in animal studies[8]. HCQ is commonly used in rheumatological conditions, such as SLE and Rheumatoid arthritis, and conditions like porphyria cutanea tarda, Q fever, and malaria. The anti-inflammatory properties of HCQ is through to be due to interference of antigen processing in macrophages and antigen presenting cells (APCs) by increasing the pH within intracellular vacuoles and endosomes[9]. Common side effects of the drug include nausea, diarrhea, QTc prolongation, and retinopathy from chronic use. CQ and HCQ have recently gained international attention for their efficacy against SARS-CoV-2 *in vitro*[10]. However, objective clinical data evaluating their use is limited. As of March 30th, 2020, the US Food & Drug Administration has issued an emergency use authorization for CQ and HCQ in adolescents and adults hospitalized for COVID who are unable to participate in clinical trials[11]. This study aims to review the literature currently available regarding the clinical use of CQ and HCQ as treatment in COVID-19 patients in an effort to catalog their recommendations and assess drug efficacy.

Methods

This is a systematic review done to analyze the current literature to find the role of CQ and HCQ in the treatment of COVID-19 patients. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used for this review[12]. This review was not registered on Prospero because data extraction began as soon as clinical trial data was made available due to the urgency of the crisis.

Eligibility Criteria:

The studies selected were:

1) Randomized or non-randomized clinical trials assessing the efficacy or safety of HCQ or CQ use in patients with COVID-19.
2) Participants in the trials could be of any age, in any geographical location.
3) Published articles, pre-print manuscripts, abstracts, letter to the editors' or currently undergoing trials.

4) Completed between December 1st, 2019 to April 26th, 2020.

The indiscriminate nature of the eligibility criteria is due to the evolving nature of the pandemic, and the limited number of completed clinical trials. The primary outcomes prioritized in this study were mortality, clinical improvement, radiological improvement, clinical complications, drug adverse events, and negative SARS-CoV-2 PCR or nasopharyngeal swab post treatment. However, any outcome analyzed by the studies was also considered.

Sources and search: Electronic search was completed using these databases:

1) Cochrane Library
2) MEDLINE
3) EMBASE
4) MedRxiv

Clinical trials that are ongoing were searched in the registry below:

1) ClinicalTrials.gov

Keywords used for searches in all databases and registry are detailed below:
"Hydroxychloroquine" + "chloroquine" and "COVID 19" + "coronavirus" + "novel coronavirus" + "SARS-CoV-2" + "COVID" + "COVID-19"
No restrictions were placed on search parameters, including status, date or language. The results of the search are detailed in Figure 1 below.

Screening:

The results of the databases and registry were searched and analyzed by two authors independently (MC and JR). Titles and abstracts were screened to isolate clinical trials utilizing HCQ or CQ as the experimental arm. Those that met eligibility requirements were read in full to extract clinical data pertaining to outcomes detailed above. Those that included HCQ or CQ specifically as therapeutic agents (rather than as prophylactic agents) were included in this review. Any discrepancies in data collection or extraction were solved by consensus with the help of a third party (JG).

Risk of bias assessment:

Risk of bias within completed clinical trials was assessed for each study using Cochrane Risk Bias Tool 2.0[13].

Summary Measures and Synthesis of Results:

It was not possible to conduct a meta-analysis given the heterogeneity of the trials included and lack of adequate data availability. Points of heterogeneity that precluded quantitative analysis included: study design (some studies were randomized while some were non-random), study protocol (some studies were intention-to-treat while others were per-protocol), variability in experimental intervention groups, variability in control intervention groups, deviation from stated intervention (some studies included additional intervention depending on clinical circumstance), and differing primary outcomes. As such, results and data are presented as an integrative qualitative review in a narrative format.

Results

Using the databases listed, initial search on April 9th, 2020 and a subsequent search on April 26th, 2020 yielded a total of 340 abstracts. Of those, 274 were eliminated as they did not meet the eligibility criteria. 66 abstracts were further investigated with their full texts analyzed. Of those full texts, 30 were eliminated as they did not use HCQ or CQ as treatment arms, but rather as prophylactic agents. The remaining 36 studies were analyzed in full, with data points extracted as per protocol. These studies included 7 completed clinical trials, which was composed of 3 pre-print texts [14 15 16], 2 published texts[17 18 19], and 1 letter of declaration[20] of results. They also included 29 ongoing clinical trials. Results and study design from completed clinical trials are detailed in Table 1a and Table 1b. Data extracted from ongoing clinical trials are detailed in the Supplemental Table S1. One publication[22] in Chinese was translated to English using Google Translator web service before review.

Risk of bias was calculated for all completed clinical trials included in this review except for Gao et al.[23], as there was no information about study design or data regarding intervention or primary outcome in the publication. Bias assessment for completed clinical trials are included below in Figure 2.

Discussion

The anti-inflammatory and antiviral properties of Chloroquine (CQ) and Hydroxychloroquine (HCQ) have been catalogued in several studies done *in vitro*[21 22 23]. The mechanism of action by which CQ and HCQ exhibit antiviral properties against SARS-CoV-2 has not be fully elucidated but presumed to be due to the alkaline nature of the drug which causes a rise in pH within endosomes in cells, leading to the prevention of viral entry and transport. In addition, CQ has previously shown an ability to block glycosylation of cell surface receptors, disabling the ability of SARS-CoV-1 to bind to angiotensin-converting enzyme 2 (ACE2) receptors which exist in abundance in human heart, lung, kidney, and intestines[24]. Since SARS-CoV-2 is thought to utilize the same mechanism for cell attachment and entry, CQ and HCQ exhibit significant promise in blocking initial viral infection *in vitro.* Given these promising *in vitro* results and the overwhelming demands of finding an effective treatment in the face of a rapidly evolving global health emergency, multiple *in vivo* clinical trials were set in motion from December 2019 to April 2020 to evaluate the efficacy of HCQ and CQ as therapeutic agents in COVID-19. Our search showed that there are presently seven such clinical trials with published or pre-published results. However, due to poor study design and haphazardly chosen outcomes, the results of these *in vivo* studies are less convincing than those *in vitro.*

The first published clinical trials evaluating antiviral activity of CQ in COVID-19 patients were from China. Gao et al.[23] published the first study in letter format, where they enlisted "more than 100 patients" and found CQ superior to control intervention (which they do not elucidate on) in clinical improvement of pneumonia, improvement of imaging findings, and shortening of disease course. This study prompted the National Health Commission of the People's Republic of China to establish the use of CQ (500mg BID for 10 days maximum) nationwide in adults with COVID-19[25]. Despite the promising results, the letter did not include any information about trial design or give any further information about the study results. It did mention that there were a "number of subsequent trials" underway to study the same intervention. Most of these trials were never completed or published, but one (Chen et al.[22]) published just 10 days later showed that an intervention of HCQ yielded no difference in clinical improvement, imaging findings, and duration of disease course versus supportive care. The Chen

et al.[22] study had its own methodological limitations, including failure to meet the minimum sample size needed for reliable analysis (i.e. n=900, study used n=30) as defined by its own protocol. There was also a lack of uniformity in the interventions, as 12/15 patients in the experimental arm and 10/15 patients in the control arm also received Abidol (an antiviral used in China). Moreover, the study demonstrated substantial risk of bias in randomization as most patients with severe illness were excluded and an exclusion criterion included ability to be excluded based upon "researcher discretion".

A recently available preprint manuscript of a study conducted by Tang et al.[16] reciprocated similar ambiguous results to that of Chen et al.[22]. In this trial, which used a larger sample size (n=150), the authors compared the anti-viral efficacy of high doses of HCQ versus standard of care and reported no significant difference in rate of negative reverse transcriptase polymerase chain reaction (RT-PCR) or time to clinical improvement. They assert that HCQ may have more potential in controlling inflammation and preventing disease progression as it led to a significant reduction in CRP (6.98 versus 2.72 in standard of care). A challenge to this assertion is the potential confounding of the results due to use of concomitant antivirals in both treatment groups. The authors acknowledged this potential confounder and report than in a *post hoc* analysis done to analyze patients who did not receive antiviral treatment, HCQ provided significant benefit in alleviation of clinical symptoms (Hazard Ratio 8.83). This *post hoc* analysis, however, had a much smaller sample size (n=28). Additionally, the trial as a whole also poses a significant risk of bias as it did not follow its intention-to-treat protocol and moved multiple patients from one intervention arm to another after randomization.

In a separate Chinese study by a different group (Chen et al.[18]), currently available as a preprint manuscript, HCQ was shown to optimize both time to clinical recovery (TTCR) and radiological improvement versus supportive care. This study was done on a group of 62 participants and both outcomes were significant ($p<0.05$). It carries less risk of bias than the previously mentioned studies, as it is the only completed study that is both double-blinded and follows an intention-to-treat protocol. Nevertheless, it still presented with significant methodological flaws. Firstly, it precluded all critical and severe cases of COVID-19 "after a doctor's evaluation", which raises concern for selection bias. Secondly, the measurement of

TTCR only included temperature and cough, foregoing analysis of oxygen exchange data, extubations, renal and hematological abnormalities, and changes in mental status. It should be noted that neither this study nor the previously published studies included any information about viral load.

The utility of HCQ and CQ has not only been compared to supportive care, but also to other emerging antiviral treatments. In another Chinese study, Huang et al.[19] showed that CQ reduced hospital stay and had greater radiological improvement of pneumonia as compared to Lopinavir/Ritonavir. While carrying important ramifications, these results are plagued with some of the same pitfalls as previous trials on CQ. Like Chen et al.[22], the sample size is small (n=22) and much of the results were statistically insignificant ($p>0.05$). Additionally, there is a significant risk of bias in randomization for this study as patients were on average much older in the CQ group (average 53.0 years) as compared to the Lopinavir/Ritonavir group (average 41.5 years). Despite these shortcomings, this trial introduces the possibility of multi-antiviral treatment of COVID-19, which is an avenue being assessed by several ongoing clinical trials (Supplemental Table S1).

While the early volume in completed clinical trials came from China, much of the international spotlight given to CQ and HCQ has stemmed from the results of a study done in Marseille, France by Gautret et al[21]. In this study, HCQ was demonstrated to be efficacious in a cohort of 42 patients by shortening time to virologic clearance as measured by RT-PCR ($p<0.05$). Moreover, HCQ plus Azithromycin (which was used in 6/20 participants in HCQ group to prevent bacterial superinfection) yielded viral clearance in 6/6 participants ($p <0.05$). However, there were major organizational and fundamental problems with this study. Firstly, the study lacked internal validity as there was no blinding or randomization. There was a significant risk of bias in recruitment of participants as all participants in the experimental arm were recruited from the same center, whereas the control arm was composed of patients from multiple centers and patients who denied experimental intervention. Furthermore, the study also did not meet the sample size needed for reliable analysis (n=48) as per its own protocol. From the patients recruited, six of the patients from the experimental arm (16.7%) were lost to follow-up or had adverse outcomes that were not included in the results. Additionally, the primary outcome

of the study (virologic clearance assessed by viral load in RT-PCR) was analyzed haphazardly, with PCR not done on each patient every day, and viral load listed for certain patients on certain days but excluded for others. The study did attempt to stratify its data according to initial presentation by layering patients into asymptomatic, lower respiratory tract infection (LRTI) and upper respiratory tract infection (URTI) groups, but the number of patients in each group was drastically asymmetric and outcomes were not assessed by group. Given these methodological limitations, the promising results of this trial come with an asterisk. The authors acknowledge that there needs to be further research with a larger cohort but give their recommendations of using HCQ plus Azithromycin. They recognize that the combination of the two drugs confers a potential risk of QTc prolongation and necessitates daily electrocardiogram monitoring for patients. Results from this study have inspired outcries from both international governing bodies and scientific communities alike to create numerous similarly designed trials to assess both HCQ and HCQ plus Azithromycin as potential therapeutic avenues (Supplemental Table S1).

One such trial was conducted by the very same authors[20]. This new study showed that use of HCQ plus Azithromycin improved clinical outcome in 65/80 patients (p value not listed). This study nevertheless contained several design flaws, similar to its predecessor. The most significant of these flaws is the lack of a control intervention. All 80 patients received HCQ plus Azithromycin with none receiving supportive care. Six of the patients included were also patients from the previous study who had already received HCQ plus Azithromycin. Additionally, the decision to discharge patients was based on a viral RT-PCR cycle threshold value, but the value was changed three times during the experiment. Despite these shortcomings, this study seems to have been an intention-to-treat protocol unlike the authors' previous study, and the authors acknowledge the need for further investigation.

Currently, of the seven completed clinical trials evaluating CQ or HCQ efficacy in treatment of COVID-19, five show that the drugs improve clinical outcome and two show no difference between the drugs and supportive care. However, all seven trials have serious methodological flaws that necessitate further investigation. There are currently several trials underway with more regimented study designs to assess safety and efficacy of these drugs (Supplemental Table S1). Although the outcomes of these studies may not be available for quite

some time, preliminary findings from select clinical trials and retrospective cohort studies are becoming available in preprint format. One such study[26], a retrospective cohort study completed using 368 patients in Veteran's Affairs centers in the US concluded that the mortality was higher in HCQ plus Azithromycin compared to supportive care (Hazard ratio: 2.61, 95% CI 1.10-6.17, p = 0.03). CQ did not fare much better as another study done in Brazil[27] (double blind, RCT) revealed that high doses of CQ (600mg BID for 10 days) conferred a higher fatality rate (27%, 95% CI= 17.9%-38.2%) compared to supportive care. Neither studies were included in data and results as they did not match the eligibility criteria (not a clinical trial or trial not completed).

Given the low cost, relatively safe side effect profile, and wide availability of CQ and HCQ as compared to other antivirals currently being tested in clinical trials there is a dire need for more evidence for their use. Thus far, there is not sufficient clinical evidence to support the routine use of HCQ or CQ in treatment of COVID-19. Some data even suggests that they confer a higher fatality rate than control. There must be more robust clinical trials in order to prove the benefit of these drugs before they are used routinely.

Limitations

The limitations of this review include a small sample of eligible clinical trials (n=7) and an indiscriminate eligibility criterion. Given the evolving nature of COVID-19, there will be more available clinical trial data with more robust study design and data points to compare to in the coming months.

Conclusion

This rapid systematic review has identified seven different completed clinical trials evaluating the efficacy of HCQ or CQ as therapy for COVID-19. The results of the trials show that HCQ or CQ is efficacious as compared to supportive care, and to Lopinavir/Ritonavir in treatment of COVID-19. However, all the studies analyzed posed significant risk for bias and had significant methodological flaws. As such, there is still a lack of clinical evidence to support therapeutic use of HCQ or CQ. There are currently several RCTs underway with more stringent study design and a greater number of participants, so pending their results, clinicians should defer from the routine use of CQ or HCQ for COVID-19.

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Table 1a: Study Design of Completed Clinical Trials Evaluating HCQ/CQ as Treatment for COVID-19

Title	Author	Publication date, Data collection dates	Institution /Country Study Conducted	Design	Inclusion criteria	Exclusion criteria	Participants	Intervention	Control	Primary Endpoint(s)	Secondary Endpoint(s)
Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial[18]	Gautret et al	Published 3/20/20, with data collected up to 3/14/20	University Hospital Institute Méditerranée Infection in Marseille, France	Open label, non-randomized clinical trial, Per-protocol analysis	• Hospitalized patients age > 12 • RT-PCR positive SARS-CoV-2	• Allergy to HCQ or CQ or contraindication to use • Breastfeeding and pregnant patients	42 patients	HCQ 600mg D1-D10 ± Azithromycin 500mg LD, 250 mg D2-D5 + Standard of care	Standard of care	• Virologic clearance at day 6	• Virologic clearance over time • Temperature • Respiratory rate • Length of hospital stay • Mortality • Side effects
A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19)[19]	Chen et al	Published 2/29/20, data collected 2/5/20-2/25/20	Shanghai Public Health Clinical Center in Shanghai, China	Open label, RCT, Intention-to-treat analysis	• Age > 18 • RT-PCR positive SARS-CoV-2	• Allergy to HCQ or CQ • Pregnancy • Heart, lung, kidney, brain, cardiovascular, or retinal disease • Hearing loss • Patients excluded by researcher's discretion	30 patients	HCQ 400mg D1-D5 + standard of care	Standard of care (included holding the treatment, and using antivirals if necessary)	• Virologic clearance at day 7 • Mortality at day 14	• Median duration of hospitalization • Body temp normalization time • Radiological progression • Adverse side effects
Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study[17]	Gautret et al	Pre-print, data collected 3/3/20 - 3/21/20	University Hospital Institute Méditerranée Infection in Marseille, France	Open label, clinical trial, no information about randomization, Intention-to-treat analysis	• Not listed	• Not listed	80 patients	HCQ 600mg D1-D10 + Azithromycin 500mg LD, 250mg D2-D5	NA	• Clinical outcome by 10 days • Contagiousness tested by RT-PCR • Length of hospital stay in ID unit	• None listed
Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial[14]	Chen et al	Preprint, data collected 2/4/20-2/28/20	Renmin hospital of Wuhan University in Wuhan, China	Double blind, RCT, Intention-to-treat analysis	• Age > 18 • RT-PCR positive SARS-CoV-2 • Chest CT showing pneumonia • SaO2/SPO2 ratio >93% • PO2/FIO2>300	• Severe and critical illness • Retinopathy • Conduction block and arrhythmias • Liver or renal disease • Pregnant • Possibility of transfer	62 patients	HCQ 400mg D1-D5 + standard of care	Standard of care	• Time to clinical recovery (TTCR) - defined as normalized body temperature and cough relief for 72+ hours,	• Radiological imaging CT (on D0 and D6)
Breakthrough Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies[20]	Gao et. al	Published 2/19/20, not stated when collected	10 hospitals in China in cities of Wuhan, Jingzhou, Guangzhou, Beijing, Shanghai, Chingqing, Ningbo	Unclear-letter of declaration of results	• Not listed	• Not listed	100 patients	CQ 500mg BID D1-D10 + Standard of care	Not listed	• Exacerbation of pneumonia • Lung imaging findings • Negative RT-PCR • Length of disease	• Adverse effects
Treating COVID-19 with Chloroquine[15]	Huang et al.	Published 4/1/20, data collected 1/27/20 - 2/15/20	Fifth Affiliated Hospital of Sun Yat-sen University in Zhuhai, China	No information about blinding, RCT, Intention-to-treat analysis	• Age ≥18 • RT-PCR positive SARS-CoV-2	• Pregnant patients • Allergies to CQ • Liver, kidney, cardiac, retinal, or hematological disease • Mental illness • Use of digitalis	22 patients	CQ 500mg BID D1-D10 + Lopinavir/ritonavir 400mg/100mg BID D1-D10	Lopinavir/ritonavir 400mg/100mg D1-D10	• RT-PCR result at day 10 and 14 • Negative conversion rate of RT-PCR	• Length of hospitalization • CT scan findings at day 10 and 14
Hydroxychloroquine in patients with COVID-19:	Tang et al.	Pre-print, data collected	16 Chinese government designated	Open label, RCT, Intention-	• Age > 18 • RT-PCR positive	• Inclusion in other trials. • Allergies to HCQ	150 patients	HCQ 1200mg LD D1-D3, 800mg D4 up to D14 for	Standard of care	• RT-PCR result on D28	• Time to alleviation of clinical symptoms

an open-label, randomized, controlled trial[16]	2/11/20-2/29/20	COVID 19 centers in 3 provinces (Hubei, Henan, Anhui)	to-treat analysis	• CT confirmation of disease severity	• Liver, renal disease or conditions that could lead to severe adverse reactions. • Cognitive impairment • Pregnant or breastfeeding		mild/moderate symptoms HCQ 1200mg LD D1-D3, 800mg D4 up to D21 for severe symptoms + Standard of care (included use of antivirals)	(included use of antivirals)	• Clinical symptoms on D7, D14, D21, D28 • Time to negative RT-PCR	• Reduction in CRP • Change in lymphocytes • Adverse effects

Abbreviations: RCT: Randomized clinical trial, LD: Loading dose, D-: Day-
Standard of care is bedrest, oxygen supplementation, and supportive care unless otherwise indicated.

Table 1b: Results of Completed Clinical Trials Evaluating HCQ/CQ as Treatment for COVID-19

Author	Group Design	Intervention	Control	Primary Endpoint(s)	Results	Comments/Problems
Gautret et al[18]	HCQ: 26 patients (6 patients lost to follow up) Control: 16 patients Grouped into 3 categories: asymptomatic, LRTI, URTI	HCQ 600mg D1-D10 ± Azithromycin 500mg LD, 250 mg D2-D5 depending on clinical presentation [6 patients received this tx to prevent bacterial super infection]	Standard of care	• Virologic clearance at day 6	HCQ group: 70% (13/20) had negative RT-PCR on day 6 Control group: 12.5% (2/16) had negative RT-PCR on day 6 HCQ+Azithromycin group: 100% (6/6) had negative RT-PCR on day 6	• Lack of internal validity; no randomization, not blind. • Intervention group all recruited from same center but control group heterogeneous • Does not follow intention-to-treat analysis. 6 patients were lost to follow-up from the experimental group. • Cases refusing protocol were used as control subjects. • Did not reach sample size needed for analysis as per own protocol (n=48). • Primary outcome (negative RT-PCR) was analyzed haphazardly with PCR not done every day on many control patients, with many fluctuations in PCR results. • Data is stratified by presenting conditions (asymptomatic, LRTI, URTI) but groups are asymmetric and not adequately assessed. • Viral loads listed for some patients, but for others only "positive" PCR listed. • Clinical outcome and adverse events not assessed.
Chen et al[19]	HCQ: 15 patients Control: 15 patients	HCQ 400mg D1-D5	Standard of care (included holding the treatment, and using antivirals if necessary)	• Virologic clearance at day 7 • Mortality at day 14	HCQ group: 86.7% (13/15) had negative RT-PCR on day 7 Medial time for temperature normalization: 1 day (95% CI 0-2 days) Radiological progression: 5 people Median duration until negative PCR: 4 days (95% CI 1-9 days) Transient diarrhea and abnormal liver function: 4/15 Control group: 93.3% (14/15) had negative RT-PCR on day 7 Medial time for temperature normalization: 1 day (95% CI 0-3 days) Radiological progression: 5 people Median duration until negative PCR: 4 days (95% CI 1-4 days) Transient diarrhea and abnormal liver function: 3/15	• Patients excluded by researcher discretion; no information given about reasons. • Study results were not statistically significant (p>0.05). • Did not reach sample size needed for analysis as per own protocol (n=900). • All patients received nebulization treatment with interferon alpha. 12/15 in the intervention group, and 10/15 in the control group received Abidol (unspecified dosage). • 2 patients received Lopinavir/Ritonavir (unspecified dosage). • No viral load data. • One patient in the intervention group did not receive a full 5 days of HCQ.
Gautret et al[17]	HCQ: 80 patients Control: None Patients were stratified by: Symptoms - 4 patients asymptomatic, 43 patients with URTI, 33 patients with LRTI National Early Warning Score (NEWS)- 69 patients with low score (0-4), 4 patients with medium score (5-6) and 2 patients with high score (>7)	HCQ 600mg D1-D10 + Azithromycin 500mg LD, 250mg D2-D5	NA	• Clinical outcome by 10 days • Contagiousness tested by nasopharyngeal viral load by RT-PCR (negative results were RNA Cycle threshold >35) and culture • Length of hospital stay in ID unit	Clinical outcome: Low NEWS: (61/69) discharged Medium NEWS: (4/4) discharged High NEWS: (0/2) discharged After 10 days, (2/80) patients were presumably contagious with Ct<34 Mean length of hospital stay: 4.6 ± 2.1 days (7/80) had adverse side effects	• No control group for study. • One patient in the intervention group did not receive a full 10 days of HCQ. • 6 of the patients included are from the author's previous study assessing HCQ+Azithromycin efficacy. • 5 patients were not assigned NEWS scores. • The vast majority of patients had low clinical severity. • Patients with pneumonia and NEWS score > 5 additionally received Ceftriaxone. • The decision to discharge patients was based on their viral load. However, the threshold value that determined discharge kept changing.

Chen et al[14]	HCQ: 31 patients Control: 31 patients	HCQ 400mg D1-D5	Standard of care	• Time to clinical recovery (TTCR) - defined as normalized body temperature and cough relief for 72+ hours,	HCQ group: TTCR: Fever length: 2.2±0.4 days, Cough length: 2.0±0.2 days 80.6% (25/31) had improved pneumonia per chest CT 2 patients had mild adverse reactions. Control group TTCR: Fever lengths: 3.2±1.3 days, Cough length: 3.1±1.5 days 54.8% (17/31) had improved pneumonia per chest CT. 4 patients progressed to severe illness.	• TTCR was measured by only temperature, and cough secession. No analysis of oxygen exchange data, extubations, changes in mental status, renal and liver abnormalities. • Analysis of chest CT progression is only based on 2 images. • Outcomes were statistically significant (p<0.05) • No viral load data. • Most critically ill patients were excluded.
Gao et. Al[20]	Not listed	CQ 500mg BID D1-D10	Standard of care	• Exacerbation of pneumonia • Lung imaging findings • Negative RT-PCR • Length of disease	No details given other than CQ is effective in improving all primary endpoints outcomes.	• No details given other than there are a number of clinical trials proving the efficacy of CQ in vivo. • No information about study design or control groups.
Huang et al.[15]	CQ: 10 patients: 3 severe 7 moderate Indinavir/Lopinavir: 12 patients: 5 severe 7 moderate	CQ 500mg BID D1-D10 + Lopinavir/ritonavir 400mg/100mg BID D1-D10	Lopinavir /ritonavir 400mg/100mg D1-D10	• RT-PCR result at day 10 and 14 • Negative conversion rate of RT-PCR	CQ group: By day 13, 100% (10/10) had negative RT-PCR CT findings: 100% (10/10) showed CT improvement at day 14 Hospital stay: 100% (10/10) discharged by day 14 9 patients had adverse events including: vomiting, abdominal pain, nausea, rash, pruritus, cough, SOB Lopinavir/Ritonavir: By day 14, 91.7% (11/12) had negative RT-PCR CT findings: 75% (9/12) showed CT improvement at day 14 Hospital stay: 50% (6/12) discharged by day 14	• Small sample size. • All outcomes were statistically insignificant (p>0.05). • No group receiving supportive treatment. • Patients receiving Lopinavir/Ritonavir treatment were on average older than CQ group (53.0 vs. 41.5) and had more severe presentations. • None of the confidence intervals given for outcomes were significant.
Tang et al.[16]	HCQ group: 75 patients enrolled 70 patients analyzed Control group: 75 patients enrolled 80 patients analyzed	HCQ 1200mg LD D1-D3, 800mg D4 up to D14 for mild/moderate symptoms HCQ 1200mg LD D1-D3, 800mg D4 up to D21 for severe symptoms + Standard of care (included use of antivirals)	Standard of care (included use of antivirals)	• RT-PCR result on D28 • Clinical symptoms on D7, D14, D21, D28 • Time to negative RT-PCR	HCQ group: RT-PCR negative D28: 85.4% (95% CI 73.8%-93.8%) Median time to negative RT-PCR: 8 days Time to alleviation of clinical symptoms: 19 days Reduction in CRP: 6.98 Absolute change of lymphocytes: 0.062 x 10^9/L Adverse effects : 30% (21/70) Control RT-PCR negative D28: 81.3% (95% CI 71.2%-89.6% P=0.34) Median time to negative RT-PCR: 8 days P=0.341 Time to alleviation of clinical symptoms: 21 days Reduction in CRP: 2.72 Absolute change of lymphocytes: 0.008 x 10^9/L Adverse effects : 8.8% (7/80) Post Hoc analysis done after removal of confounder (anti-virals) Alleviation of clinical symptoms: HCQ showed better efficacy Hazard ratio: 8.83 (95 CI 1.09-71.3)	• Trial listed as intention-to-treat protocol, but 6 patients from HCQ group moved to control, and 1 patient from control group moved to HCQ group. • Did not reach sample size needed for analysis as per own protocol (n=260) • Dosing of HCQ deviated from stated dose in some patients due to adverse effects but details of adjustment not provided in preprint copy. • Standard of care included administration of concomitant antiviral medications, but medications not listed. • Mean days of disease onset to randomization: 16.6 ± 10.5 days. • Only points of significance in outcome were reduction in CRP (p=0.045) and adverse effects (p=.0001) • Post-hoc analysis done to remove confounding by antivirals administered.

Abbreviations: RCT: Randomized clinical trial, LD: Loading dose, D-: Day-
Standard of care is bedrest, oxygen supplementation, and supportive care unless otherwise indicated.

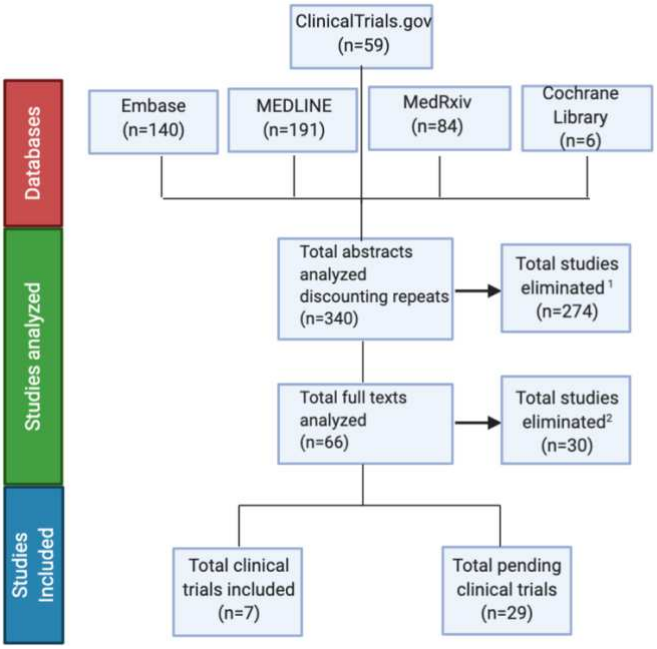

Figure 1: Flowchart detailing study selection

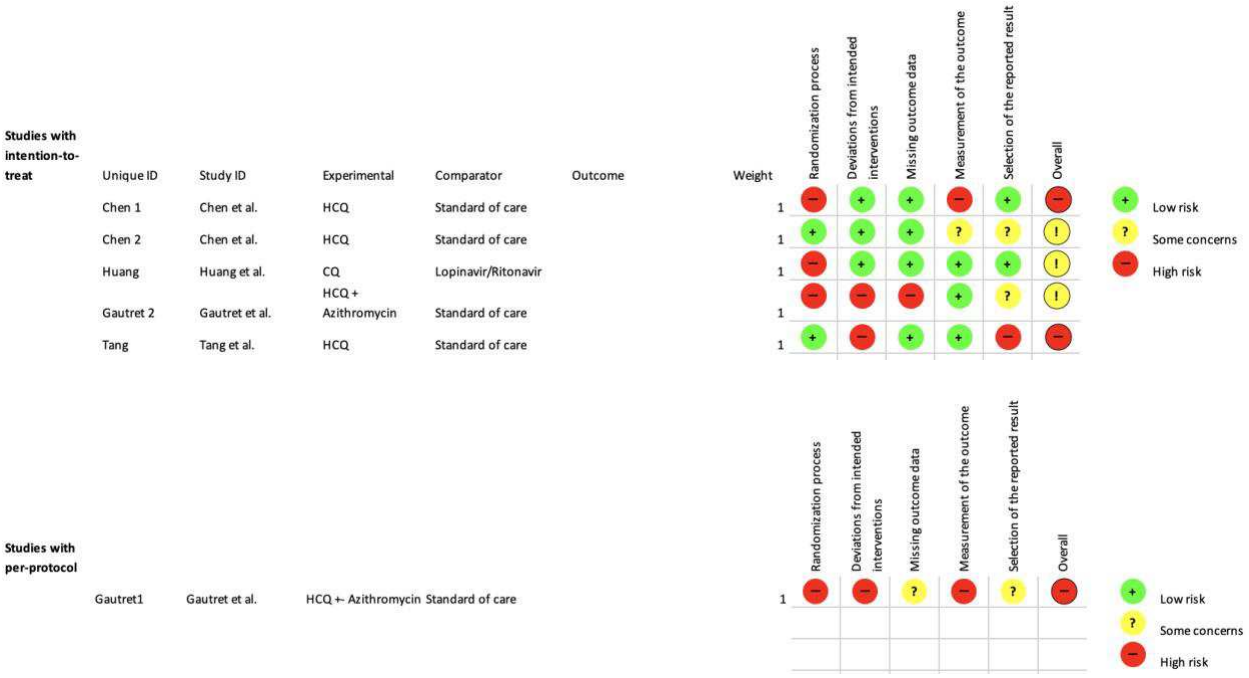

Figure 2: Risk of Bias in Completed Clinical Trials Measuring HCQ/CQ Efficacy