Efficacy of early treatment with hydroxychloroquine in people with mild to moderate COVID-19: A systematic review and meta-analysis

Type
Research paper

Keywords
safety, early treatment, COVID-19, efficacy, Hydroxychloroquine

Abstract

Introduction
No early treatment intervention for COVID-19 has proven effective to date. We systematically reviewed the efficacy of hydroxychloroquine as early treatment for COVID-19.

Material and methods
Randomized controlled trials (RCTs) evaluating hydroxychloroquine for early treatment of COVID-19 were searched in five engines and preprint websites until September 14, 2021. Primary outcomes were hospitalization and all-cause mortality. Secondary outcomes included COVID-19 symptom resolution, viral clearance, and adverse events. Inverse variance random-effects meta-analyses were performed and quality of evidence (QoE) per outcome was assessed with GRADE methods.

Results
Five RCTs (n=1848) were included. The comparator was placebo in four RCTs and usual care in one RCT. The RCTs used hydroxychloroquine total doses between 1,600 and 4,400 mg and had follow up times between 14 and 90 days. Compared to the controls, early treatment with hydroxychloroquine did not reduce hospitalizations (RR 0.80, 95%CI 0.47-1.36, I²=2%, 5 RCTs, low QoE), all-cause mortality (RR 0.77, 95%CI 0.16-3.68, I²=0%, 5 RCTs, very low QoE), symptom resolution (RR 0.94, 95%CI 0.77-1.16, I²=71%, 3 RCTs, low QoE) or viral clearance at 14 days (RR 1.02, 95%CI 0.82-1.27, I²=65%, 2 RCTs, low QoE). There was a higher non-significant increase of adverse events with hydroxychloroquine vs. controls (RR 2.17, 95%CI 0.86-5.45, I²=92%, 5 RCTs, very low QoE).

Conclusions
Hydroxychloroquine was not efficacious as early treatment for COVID-19 infections in RCTs with low to very low quality of evidence for all outcomes. More RCTs are needed to elucidate the efficacy of hydroxychloroquine as early treatment intervention.
Efficacy of early treatment with hydroxychloroquine in people with mild to moderate COVID-19: A systematic review and meta-analysis

Running head: Hydroxychloroquine for COVID-19
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Keywords: Hydroxychloroquine; COVID-19; efficacy; safety; early treatment
Introduction

Over 43 million people in the United States (US) have contracted COVID-19 resulting in ~698,000 deaths [1]. The surges in cases have brought with it over 3,000,000 hospitalizations that threaten to overwhelm the strained healthcare system [1]. One approach to reducing the impact of COVID-19 on the healthcare system is through early treatment of patients in the outpatient setting.

The monoclonal antibodies products bamlanivimab [2] and casirivimab/indevimab [3] recently received emergency use authorization from the Food and Drug Administration (FDA) for the treatment of COVID-19 patients at high risk for progressing to hospitalization. While these early treatment trials were positive, bamlanivimab was found inefficacious for the treatment of hospitalized COVID-19 patients [4], supporting the hypothesis that antiviral therapy is most effective early in the course of disease [5].

The results of hydroxychloroquine randomized controlled trials (RCTs) and cohort studies for the treatment of hospitalized patients have been lackluster [6,7] and its emergency use authorization was revoked by the FDA [8]. However, at the November 2020 American Medical Association meeting, delegates tried to get the organization to revoke its statement discouraging the use of hydroxychloroquine for COVID-19, especially for the early outpatient treatment of the disease [9]. That same month, several panelists at a US Senate hearing touted hydroxychloroquine’s outpatient use in COVID-19, and asked for its emergency use authorization to be reinstated [10]. If hydroxychloroquine is effective and safe in the early treatment of COVID-19, it would be markedly less expensive than monoclonal antibody therapy and much more readily available to roll out to the general public. However, the use of hydroxychloroquine may have adverse events and shunting utilization to COVID-19 patients
could cause shortages for those patients who need hydroxychloroquine for autoimmune diseases and malaria [11].

In this systematic review with meta-analyses, we assessed the efficacy and safety of hydroxychloroquine in early onset treatment of COVID-19 from all the available randomized controlled trials.

**Methods**

**Data Sources and Searches**

Three investigators (C.M.W., V.P., and A.V.H.) developed the search strategy, which was revised and approved by the other investigators. We searched the following databases from December 01, 2019 to September 14, 2021: PubMed-MEDLINE, EMBASE-OVID, Scopus, Web of Science, the Cochrane Library, bioRxiv (www.biorxiv.org), Preprints (www.preprints.org), Clinical Trials.gov, the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/en/), and the Chinese Clinical Trials Registry (www.chictr.org.cn). The PubMed search strategy is shown in the **Supplemental file**.

**Study Selection**

We included randomized controlled studies (RCTs) in any language reporting benefit or harm outcomes from use of hydroxychloroquine as early treatment (i.e. a few days from symptom onset to enrolment) in outpatients with mild to moderate reverse transcription-polymerase chain reaction (RT-PCR)-confirmed COVID-19. We excluded studies in hospitalized COVID-19 patients, even though patients had mild to moderate disease and/or early disease, studies of prophylaxis with hydroxychloroquine (i.e. in those without COVID-19 disease), and cohort
studies evaluating hydroxychloroquine as early treatment of COVID-19. Three investigators (A.V.H., V.P., Y.M.R.) independently screened each record title and abstract for potential inclusion. Three investigators (V.P., J.J.B., Y.M.R.) then read the full text of the records whose abstracts had been selected by at least one investigator. Discrepancies were resolved through discussion or by a fourth investigator (A.V.H.).

**Outcomes**

Primary outcomes were hospitalization and all-cause mortality. Secondary outcomes were intensive care unit (ICU) admission, need of mechanical ventilation, COVID-19 symptom resolution, viral clearance in nasopharyngeal swabs, adverse events, and specific adverse events (e.g. diarrhea, headache, QTc prolongation).

**Data Extraction**

Two investigators (A.P., J.J.B.) independently extracted the following variables from studies: study setting, country, mean age, proportion of male, time from symptom onset in days, proportion of chronic coexisting diseases, hydroxychloroquine dose and duration, type of control and description, additional drug interventions, primary and secondary outcomes, and time of follow up. Discrepancies were resolved through discussion or by a third investigator (A.V.H.).

**Risk of bias assessment**

Two investigators (A.P., J.J.B.) independently assessed risk of bias (RoB) of randomized controlled trials with the Cochrane Risk of Bias 2.0 tool for RCTs [12,13]; disagreements were resolved by discussion with a third investigator (A.V.H.). RoB 2 assesses five domains: bias due
to the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. RoB of each domain and each RCT was described as low, some concerns or high.

**Statistical analyses**

We reported our systematic review according to 2009 PRISMA guidelines [14]. Inverse variance random effect meta-analyses were performed to evaluate effect of hydroxychloroquine vs. control on outcomes when outcome data was available for at least two RCTs or cohorts judged to have homogeneous study characteristics. Effects of meta-analyses were reported as relative risks (RR) for dichotomous outcomes and as mean differences (MD) for continuous outcomes, along with their 95% confidence intervals (CIs). CIs of effects were adjusted with the Hartung-Knapp method [15], and the between study variance tau^2 was calculated with the Paule-Mandel method. Heterogeneity of effects among studies was quantified with the I^2 statistic (an I^2>60% means high heterogeneity). The *meta* package of R 3.5.1 (www.r-project.org) was used for meta-analyses. The quality of evidence (QoE) was evaluated using the GRADE methodology, which covers five aspects: risk of bias, inconsistency, indirectness, imprecision, and publication bias [16]. Quality of evidence was evaluated per outcome and described in summary of findings (SoF) tables; GRADEpro GDT was used to create SoF tables [17].

**Results**

**Selection of studies**

Our comprehensive search yielded 9551 citations with an additional 927 citations identified through other sources, including backwards citation tracking. After removing duplicates and
applying our inclusion and exclusion criteria (Fig. S1), we identified five RCTs [18-22] (n=1848) which were all homogenous enough to warrant meta-analyses.

**Characteristics of included studies**

The general characteristics of the included RCTs are included in Table I. Placebo was the comparator in four RCTs [19-22] while usual care was the comparator in the open label one [18]. The five RCTs used hydroxychloroquine total doses between 1,600 and 4,400 mg and had follow up times between 14 and 90 days. Mean or median ages ranged between 37 and 53 years-old, males between 31% and 55%, median time of COVID-19 symptom onset between 3 and 7 days, with most of individuals within 9 days of symptom onset, and the proportion of individuals without coexisting disease between 36% and 68%.

**Risk of bias of included studies**

One RCT had high risk of bias due to missing outcome data [19], two RCTs had some concerns of bias due to deviations from intended interventions and selection in the reported result [18] and due to bias in the randomization process [21], and two RCTs had low risk of bias [20,22] (Fig. S2).

**Effects of early treatment with hydroxychloroquine on outcomes**

In comparison to the control group, hydroxychloroquine non-significantly reduced hospitalizations by 20% (RR 0.80, 95%CI 0.47-1.36, I²=2%, 5 RCTs, low QoE, Fig. 1) and all-cause mortality by 23% (RR 0.77, 95%CI 0.16-3.68, I²=0%, 5 RCTs, very low QoE, Fig. 2). Also, hydroxychloroquine had no effect on COVID-19 symptom resolution (RR 0.94, 95%CI
0.77-1.16, I²=71%, 3 RCTs, low QoE, Fig. S3), time to COVID-19 symptom resolution (MD -0.16 days, 95% CI -4.56 to 4.25 days, I²=80%, 2 RCTs, very low QoE, Fig. S4) and on viral clearance at 14 days (RR 1.02, 95% CI 0.82-1.27, I²=65%, 2 RCTs, low QoE, Fig. S5) in comparison to the control group.

There was no data about ICU admissions or need of mechanical ventilation in RCTs. Hydroxychloroquine non-significantly increased risks of adverse events in comparison to the control group (RR 2.17, 95% CI 0.86-5.45, I²=92%, 5 RCTs, very low QoE, Fig. 3). There was very scarce report of specific adverse events in the RCTs.

**Quality of evidence of effects**

The quality of evidence was low to very low for all outcomes (Table II). The main drivers of poor quality of evidence in RCTs were high risk of bias, imprecision of effects and inconsistency.

**Discussion**

In our systematic review we found that hydroxychloroquine as early treatment for COVID-19 was not associated with lower hospitalization, all-cause mortality, or overall adverse events risks vs. controls (usual care or placebo) in five RCTs. There was no effect of hydroxychloroquine on COVID-19 symptom resolution or viral clearance at 14 days. No data on other outcomes such as ICU admissions, need for mechanical ventilation, or specific adverse events was reported. The quality evidence was low to very low in all outcomes.

The 20% relative reductions in hospitalizations in RCTs is encouraging, especially since three of the biggest RCTs had the same direction of effect in favor of hydroxychloroquine but
none of the individual risks was significant across RCTs. If this were a real benefit of therapy, reducing relative risks of hospitalizations in those recently contracting COVID-19 by one fifth would make a difference in the overstressed healthcare system. However, more RCTs of higher methodologic quality are needed for us to adequately assess this outcome with the use of early treatment with hydroxychloroquine in the future.

The RCTs found no impact on all-cause mortality; probable reasons included scarcity of events (i.e. one event per arm in Skipper et al. [19] and one event in the control arm in Reis et al. [21]), and also short time of follow up as Skipper et al. [19] only had a 14-day, Mitjà et al. [18] and Johnston et al. [20] only had 28 days, and Schwartz et al. [22] only had 30 days, so it could have been too soon to see mortality reductions. The dose of hydroxychloroquine therapy was not a viable explanation for the lack of effect on all-cause mortality across RCTs as the total doses in the RCTs ranged from 3,200 mg to 4,400 mg, with the exception of the small RCT by Schwartz et al. [22] with 1,600 mg of total dose. The duration of hydroxychloroquine was not a viable explanation either with RCTs providing hydroxychloroquine therapy for 5 to 9 days. Three recent systematic reviews and meta-analyses including RCTs until October 16, 2020 did not evaluate mortality effects of hydroxychloroquine in outpatients [23-25]; two other recent systematic reviews and meta-analyses including RCTs until October 15, 2020 [26,27] only assessed mortality effects in COVID-19 outpatients using the Mitja et al. [18] and Skipper et al. [19] RCTs.

Hydroxychloroquine for the early treatment of COVID-19 would compete against the monoclonal antibody products bamlanivimab [2] and casirivimab/indevimab [3] that were recently received emergency use authorization from the FDA for the treatment of COVID-19 patients at high risk for progressing to hospitalization. These drugs will cost between $1,250 and
$1,500 per dose according to governmental contracts. Bamlanivimab was authorized based on the results from the ‘Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies’ (BLAZE-1) RCT [28]. In the combined bamlanivimab dosing group, the incidence of hospitalizations or emergency department visits was non-significantly lower (3 of 309 [1.6%] vs. 9 of 143 [6.3%]) by day 29. In a 799-patient trial that is still unpublished [29], treatment with casirivimab/indevimab was associated with a 57% reduction in COVID-19-related medical visits through day 29, which was significantly greater than the placebo group (p=0.024).

The National Institutes of Health COVID-19 Treatment Guideline Panel [2] has cautioned that there is insufficient evidence of bamlanivimab’s efficacy in early outpatient treatment and has not commented on the use of casirivimab/indevimab because the data is unpublished. As such, we cannot determine if any of these therapies is truly beneficial in the early treatment of COVID-19 or if one option is superior to the others. If hydroxychloroquine is subsequently found to significantly reduce hospitalizations, it would offer several advantages over monoclonal antibody therapy including better established safety profile, lower acquisition cost, more convenient dosing form, and more ample supply for COVID-19 patients.

However, if hydroxychloroquine is not truly efficacious or effective, the adverse events associated with therapy would not be balanced out with benefits and shunting the drug supply away from patients with autoimmune diseases could negatively impact other patients in the healthcare system. In a study of 3,872 patients taking hydroxychloroquine or chloroquine for autoimmune diseases [11], 27%, 21%, 7%, and 2% of patients in Africa, South-East Asia, North and South America and Europe, respectively, reported running out of medication due to drug shortages in the COVID-19 era. These patients experienced poorer physical (5.6 < 6.4, t(254) =
5.97, p<0.001) and mental (5.8 < 6.3, t(252) = 3.82, p<0.001) health and higher levels of rheumatic disease activity (5.1 > 4.3, t(244) = 4.44, p<0.001) as a result.

Our study has several limitations. First, all outcomes had low to very low quality of evidence mainly explained by heterogeneity of effects across trials, high risk of bias or some concerns of bias of three RCTs, and imprecision of effects. Second, there was very scarce all-mortality data across RCTs, and only two or three RCTs had information on symptom resolution or viral clearance. Third, there was no data on ICU admissions, need of mechanical ventilation, or specific adverse events. Fourth, four of the five RCTs [19-22] had fewer patients randomized than originally planned; this may have been resulted in lack of power to detect effects of hydroxychloroquine on outcomes. Finally, we did not evaluate the effect of adding azithromycin to hydroxychloroquine in our study.

Conclusion

Hydroxychloroquine as early treatment did not reduce hospitalizations, all-cause mortality, COVID-19 symptom resolution, and viral clearance in COVID-19 outpatients from five RCTs in comparison to placebo or usual care. There also was a non-significant increase in adverse events with hydroxychloroquine as early treatment. There was no data for outcomes such as ICU admission, need of mechanical ventilation or specific adverse events. The quality of evidence was low to very low for all outcomes.

Given its low acquisition cost, relative safety, convenient administration route, and available supply, hydroxychloroquine should continue to be investigated for outpatients who test positive for COVID-19. However, hydroxychloroquine should not be recommended for acute
treatment at this time because the balance of benefits to harms cannot be determined given the current literature base.

**Disclosure statement:** The authors declare no conflict of interest.

**References**


29. May B. Regeneron’s REGN-COV2 Cocktail Meets Clinical Endpoints in Phase II/III Trial. 10/30/2020. Available at: https://www.biospace.com/article/regeneron-s-regn-
Figure Legends

Figure 1: Effect of early treatment with HCQ on hospitalization.

Figure 2: Effect of early treatment with HCQ on all-cause mortality.

Figure 3: Effect of early treatment with HCQ on adverse events.
SUPPLEMENTAL FILE

Efficacy and effectiveness of early treatment with hydroxychloroquine in people with mild to moderate COVID-19: A systematic review and meta-analysis

Supplemental Methods: PubMed Search Strategy

Figure S1: Flowchart of study selection

Figure S2: Risk of bias assessment of randomized controlled trials

Figure S3: Effect of early treatment with HCQ on COVID-19 symptom resolution by 14 to 30 days.

Figure S4: Effect of early treatment with HCQ on time to COVID-19 symptom resolution in days.

Figure S5: Effect of early treatment with HCQ on viral clearance at 14 days.
**PubMed Search strategy**

**Figure S1:** Flowchart of study selection

- Records identified through database searching (n = 9552)
- Additional records identified through other sources (n = 927)

**Records after duplicates removed** (n = 6139)

- Records screened (n = 6139)
- Records excluded (n = 5962)

- Full-text articles assessed for eligibility (n = 177)

- Studies included in qualitative synthesis (n = 5)

- Studies included in quantitative synthesis (meta-analysis) (n = 5)

- Full-text articles excluded, with reasons (n = 172)
  - 22 cohorts of HCQ hospital treatment
  - 10 RCTs of HCQ hospital treatment
  - 132 uncontrolled studies of HCQ hospital treatment
  - 5 HCQ prophylaxis studies
  - 3 HCQ early treatment cohorts
Figure S2: Risk of bias assessment of randomized controlled trials

![Risk of bias assessment](image-url)
Figure S3: Effect of early treatment with HCQ on COVID-19 symptom resolution by 14 to 30 days.

<table>
<thead>
<tr>
<th>Source</th>
<th>Hydroxychloroquine Events</th>
<th>Total Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>RR [95%-CI]</th>
<th>Favors Control</th>
<th>Favors HCQ</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skipper 2020</td>
<td>152</td>
<td>201</td>
<td>135</td>
<td>194</td>
<td>1.09 [0.96; 1.23]</td>
<td></td>
<td></td>
<td>45.0%</td>
</tr>
<tr>
<td>Johnston 2021</td>
<td>30</td>
<td>60</td>
<td>38</td>
<td>72</td>
<td>0.95 [0.68; 1.32]</td>
<td></td>
<td></td>
<td>22.4%</td>
</tr>
<tr>
<td>Schwartz 2021</td>
<td>67</td>
<td>111</td>
<td>29</td>
<td>37</td>
<td>0.77 [0.61; 0.97]</td>
<td></td>
<td></td>
<td>32.6%</td>
</tr>
</tbody>
</table>

Random effects model 249 372 202 303 0.94 [0.77; 1.16] 100.0%

Heterogeneity: $i^2 = 71\%$, $q^2 = 0.0210$, $p = 0.03$
**Figure S4:** Effect of early treatment with HCQ on time to COVID-19 symptom resolution in days.

<table>
<thead>
<tr>
<th>Source</th>
<th>Hydroxychloroquine</th>
<th>Control</th>
<th></th>
<th></th>
<th></th>
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<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>MD [95%-CI]</td>
<td>Favors HCQ</td>
<td>Favors Control Weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milja 2020</td>
<td>10.50</td>
<td>10.4000</td>
<td>136</td>
<td>12.80</td>
<td>11.1000</td>
<td>157</td>
<td>-2.30 [-4.76; 0.16]</td>
<td>52.4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schwartz 2021</td>
<td>14.50</td>
<td>7.4000</td>
<td>89</td>
<td>12.30</td>
<td>8.2000</td>
<td>35</td>
<td>2.20 [-0.92; 5.32]</td>
<td>47.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Random effects model 225

Heterogeneity: $I^2 = 80\%$, $\tau^2 = 8.0668$, $p = 0.03$
**Figure S5:** Effect of early treatment with HCQ on viral clearance at 14 days.

<table>
<thead>
<tr>
<th>Source</th>
<th>Hydroxychloroquine</th>
<th>Control</th>
<th>RR [95%-CI]</th>
<th>Favors Control</th>
<th>Favors HCQ</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnston 2021</td>
<td>43 49</td>
<td>40 52</td>
<td>1.14 [0.95; 1.37]</td>
<td></td>
<td></td>
<td>50.1%</td>
</tr>
<tr>
<td>Reis 2021</td>
<td>97 185</td>
<td>112 195</td>
<td>0.91 [0.76; 1.10]</td>
<td></td>
<td></td>
<td>49.9%</td>
</tr>
</tbody>
</table>

Random effects model: 140 234 152 247 1.02 [0.82; 1.27] 100.0%

Heterogeneity: $I^2 = 65\%$, $\chi^2 = 0.0162$, $p = 0.09$
Table I. Baseline characteristics of randomized controlled studies included in the systematic review

<table>
<thead>
<tr>
<th>Author, Year [ref]/ Type of study/ Registration</th>
<th>Objective</th>
<th>Sample, Country</th>
<th>Population</th>
<th>Overall Key Patient Characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
<th>Follow up time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitjà et al., 2020 [18], Parallel RCT, NCT04304053</td>
<td>To determine whether early treatment with HCQ would be more efficacious than no-treatment for outpatients with mild COVID-19.</td>
<td>293 (I: 136, C: 157), Spain</td>
<td>Adult (&gt;=18 years) patients who had mild symptoms of COVID-19 (i.e., fever, acute cough, shortness of breath, sudden olfactory or gustatory loss, or influenza-like illness) for &lt;5 days before enrollment, were non-hospitalized, and had a positive PCR test for SARS-CoV-2 in the baseline NP swab. Mean (SD) age: 41.6 (12.6) years. Male: 31%. Median (IQR) time from symptom onset to enrolment: 3 (2-4) days. No coexisting disease: 47%.</td>
<td>HCQ 800 mg on day 1, followed by 400 mg once daily for 6 days (3,200 mg total dose). Initially, the protocol used HCQ plus cobicistat-boosted darunavir (DRVc) combined treatment, but it was adapted to HCQ alone.</td>
<td>Usual care (no details provided)</td>
<td>Primary: Viral RNA load in NP swabs at days 3, and 7 after treatment start. Secondary: Clinical progression with simplified version of WHO progression scale of 4 points, time from randomization to complete resolution of symptoms within the 28 days, resolution of symptoms, severe adverse events.</td>
<td>28 days</td>
<td></td>
</tr>
<tr>
<td>Skipper et al. 2020 [19], Parallel RCT, NCT0408668</td>
<td>To investigate whether HCQ could reduce COVID-19 severity in adult outpatients.</td>
<td>491 (I: 212, C: 211), USA and Canada</td>
<td>Non-hospitalized adults (&gt;=18 years) with &lt;=4 days of symptoms and either PCR-confirmed SARS-CoV-2 infection or symptoms after a high-risk exposure to a PCR-confirmed COVID-19 person within the past 14 days. HCW who had COVID-19 symptoms and high-risk exposure but whose contact had PCR results pending. Participants with a high-</td>
<td>Median (IQR) age: 40 (32-50) years. Male: 44%. Proportion with duration of symptoms onset to enrolment &lt;=2 days: 74%. No coexisting disease: 68%.</td>
<td>HCQ 800 mg (4 tablets) once, then 600 mg 6 to 8 hours later, then 600 mg once daily for 4 more days (5 days in total) (3,800 mg total dose).</td>
<td>Placebo tablets of folic acid (400 ug) prescribed as an identical regimen.</td>
<td>Original primary: Ordinal outcome by day 14 of not hospitalized, hospitalized, or ICU stay or death. Modified primary: Change in overall symptom severity over 14 days measured on a 10-point VAS. Secondary: Symptom severity at day 5 and day 14 by 10-point VAS, incidence of all hospitalizations and 14 days</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Table</td>
<td>Age</td>
<td>Male</td>
<td>Risk Factors</td>
<td>Intervention</td>
<td>Primary</td>
<td>Secondary</td>
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<tr>
<td>Johnston et al. 2021 [20], cluster RCT, NCT04354428</td>
<td>To evaluate the efficacy of HCQ and HCQ+AZ to prevent progression of COVID-19 among high- and low-risk outpatients with COVID-19</td>
<td>231 (HCQ: 71, HCQ+AZ: 77, P: 83), USA</td>
<td>Age between 18 and 80 years, lab-confirmed SARS-CoV-2 infection within the prior 72h. High-risk group: established risk factors for severe COVID-19 (age ≥ 60, pulmonary disease, DM, HTN, BMI ≥ 30). Low risk group: did not meet any high-risk criteria.</td>
<td>Median (min-max) age: 37 (18-78) years. Male: 43%</td>
<td>HCQ 400mg day 1, then 200 mg twice daily for 9 days (4,000 mg total dose). HCQ 400mg + AZ 500mg day 1, then HCQ 200mg twice daily for 9 days + AZ 250mg once daily for 4 days (HCQ 4,000 mg total dose + AZ 1,500 total dose).</td>
<td>Placebo-equivalent (ascorbic acid [500mg day 1, 250mg twice daily for 9 days] + folic acid [800ug day 1, 400ug twice daily for 4 days]).</td>
<td>Primary: Composite of 14-day development of LRTI (SpO₂ &lt; 93% on two readings with symptoms), 28-day COVID-19 related hospitalization or death; 14-day time to viral clearance. Secondary: Time to symptom resolution by day 14 among those who had COVID-19 symptoms at baseline; adverse events.</td>
<td>28 days</td>
</tr>
<tr>
<td>Reis et al. 2021 [21], parallel RCT, NCT04403100</td>
<td>To determine whether HCQ or L/R reduces hospitalization among high-risk patients with early symptomatic COVID-19 in an outpatient setting.</td>
<td>685 (HCQ: 214, L/R: 244, P: 227), Brazil</td>
<td>18 years or older, reported &lt;8 days since onset of flulike symptoms or chest CT scan consistent with COVID-19, lab-confirmed SARS-CoV-2 infection, and at least one criterion for high risk: ≥ 50 years, pulmonary disease (moderate or severe asthma, COPD, pulmonary HTN, or emphysema), DM, HTN, known CVD, BMI ≥ 30.</td>
<td>Median (IQR) age: 53 (18-94) years. Male: 45%</td>
<td>HCQ 800mg day 1, then 400mg for 9 days (4,400 mg total dose) L/R 800/200mg first two intakes, then 400/100mg twice a day for 9 days (5,200/1,300 mg total dose).</td>
<td>Placebo (inert material-talc); bottles were identical to HCQ or L/R.</td>
<td>Primary: COVID-associated hospitalization; death. Both measured at 90 days. Secondary: Hospital admission for any cause; proportion of persons with clearance of SARS-CoV-2 at days 3, 7, and 14; time to symptom resolution; treatment emergent adverse events.</td>
<td>90 days</td>
</tr>
<tr>
<td>Study</td>
<td>Objective</td>
<td>Design</td>
<td>Medication</td>
<td>Primary Outcome</td>
<td>Secondary Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
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<td>------------</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schwartz et al. 2021 [22], parallel RCT, NCT04329611</td>
<td>To determine whether HCQ treatment for outpatients with SARS-CoV-2 infection could prevent hospitalization, mechanical ventilation or death.</td>
<td>Adults with SARS-CoV-2 infection confirmed by RT-PCR from a NP or pharyngeal swab within the previous 4 days, with symptom onset within the previous 12 days, and with ≥1 risk factor for severe disease (receiving immunosuppressants or biologic therapies, age≥40, BMI&gt;40, chronic lung disease, HTN, DM, CVD, CKD, cancer, transplant recipient, severe immune suppression, smoking)</td>
<td>Mean (SD) age: 46.8 (11.3) years Male: 55% Median (IQR) time from symptom onset to randomization: 7 (5-9) days. Low risk (age 40-64y with no other risk factors): 36%</td>
<td>HCQ 800mg day 1, then 200mg twice daily for 4 days (1,600 mg total dose)</td>
<td>Matching placebo (12 tablets over 5 days)</td>
<td>Primary: Severe disease (composite of hospitalization, invasive mechanical ventilation or death within 30 days). Secondary: Days to symptom resolution; disposition at 30 days (recovered, symptomatic non-hospitalized, hospitalized, admitted to ICU, dead); serious adverse events.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

COVID-19: Coronavirus disease 2019; I: Intervention; C: Comparator; P: Placebo; HCQ: Hydroxychloroquine; AZ: Azithromycin; L/R: lopinavir/ritonavir; NP: Nasopharyngeal; CT: Computed tomography; HCW: Health care worker; RT-PCR: Reverse transcriptase polymerase chain reaction; ICU: Intensive care unit; VAS: Visual analogue scale; SC: Standard of care; NA: Not available; min: minimum; max: maximum; DM: diabetes mellitus; HTN: hypertension; COPD: Chronic obstructive pulmonary diseases; CVD: cardiovascular diseases; CKD: Chronic kidney disease; BMI: body mass index; LRTI: lower respiratory tract infection;
Table II. Summary of findings table for the effects of early treatment with hydroxychloroquine vs. control in COVID-19 patients.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>№ of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization follow-up: range 14 days to 90 days</td>
<td>5 per 100 (2 to 6)</td>
<td>RR 0.80 (0.47 to 1.36)</td>
<td>1458 (5 RCTs)</td>
<td>⬤⬤◯◯ Low(^a)</td>
</tr>
<tr>
<td>All-cause mortality follow-up: range 14 days to 90 days</td>
<td>0 per 100 (0 to 1)</td>
<td>RR 0.77 (0.16 to 3.68)</td>
<td>1431 (5 RCTs)</td>
<td>⬤◯◯◯ Very low(^a,b)</td>
</tr>
<tr>
<td>COVID-19 symptom resolution follow-up: range 14 days to 30 days</td>
<td>67 per 100 (51 to 77)</td>
<td>RR 0.94 (0.77 to 1.16)</td>
<td>675 (3 RCTs)</td>
<td>⬤⬤◯◯ Low(^c,d)</td>
</tr>
<tr>
<td>Time to COVID-19 symptom resolution assessed with: days follow-up: range 28 days to 30 days</td>
<td>The mean time to COVID-19 symptom resolution was 12.7 days</td>
<td>MD 0.16 days lower (4.56 lower to 4.25 higher)</td>
<td>-</td>
<td>⬤◯◯◯ Very low(^e,f,g)</td>
</tr>
<tr>
<td>Viral clearance assessed with: RT-PCR from nasopharyngeal swab follow-up: mean 14 days</td>
<td>62 per 100 (50 to 78)</td>
<td>RR 1.02 (0.82 to 1.27)</td>
<td>481 (2 RCTs)</td>
<td>⬤⬤◯◯ Low(^h,i)</td>
</tr>
<tr>
<td>Adverse events follow-up: range 14 days to 28 days</td>
<td>15 per 100 (13 to 83)</td>
<td>RR 2.17 (0.86 to 5.45)</td>
<td>1495 (5 RCTs)</td>
<td>⬤◯◯◯ Very low(^a,i,k)</td>
</tr>
</tbody>
</table>
Explanations

a. Very serious risk of bias due to high risk of bias in Skipper 2020 due to missing outcome data, and some concerns of bias in Mitja 2020 due to deviations from intended interventions and selection of the reported results and in Reis 2021 due to bias in the randomization process.

b. Serious imprecision as 95%CI of RR was 0.16 to 3.68

c. Serious risk of bias due to high risk of bias in Skipper 2020 due to missing outcome data.

d. Serious heterogeneity of effects across trials as I²=71%.

e. Serious risk of bias due to some concerns of bias in Mitja 2020 due to deviations from intended interventions and selection of the reported results.

f. Very serious heterogeneity of effects across trials as I²=80%.

g. Serious imprecision as 95%CI of MD was -4.56 to 4.25 days

h. Serious risk of bias due to some concerns of bias of the randomization process in Reis 2021.

i. Serious heterogeneity of effects between trials as I²=65%.

j. Very serious heterogeneity of effects across trials as I²=92%.

k. Serious imprecision as 95%CI of RR was 0.86 to 5.45
Efficacy of early treatment with hydroxychloroquine in people with mild to moderate COVID-19: A systematic review and meta-analysis

Running head: Hydroxychloroquine for COVID-19
Abstract

Introduction: No early treatment intervention for COVID-19 has proven effective to date. We systematically reviewed the efficacy of hydroxychloroquine as early treatment for COVID-19.

Materials and Methods: Randomized controlled trials (RCTs) evaluating hydroxychloroquine for early treatment of COVID-19 were searched in five engines and preprint websites until September 14, 2021. Primary outcomes were hospitalization and all-cause mortality. Secondary outcomes included COVID-19 symptom resolution, viral clearance, and adverse events. Inverse variance random-effects meta-analyses were performed and quality of evidence (QoE) per outcome was assessed with GRADE methods.

Results: Five RCTs (n=1848) were included. The comparator was placebo in four RCTs and usual care in one RCT. The RCTs used hydroxychloroquine total doses between 1,600 and 4,400 mg and had follow up times between 14 and 90 days. Compared to the controls, early treatment with hydroxychloroquine did not reduce hospitalizations (RR 0.80, 95%CI 0.47-1.36, I²=2%, 5 RCTs, low QoE), all-cause mortality (RR 0.77, 95%CI 0.16-3.68, I²=0%, 5 RCTs, very low QoE), symptom resolution (RR 0.94, 95%CI 0.77-1.16, I²=71%, 3 RCTs, low QoE) or viral clearance at 14 days (RR 1.02, 95%CI 0.82-1.27, I²=65%, 2 RCTs, low QoE). There was a higher non-significant increase of adverse events with hydroxychloroquine vs. controls (RR 2.17, 95%CI 0.86-5.45, I²=92%, 5 RCTs, very low QoE).

Conclusions: Hydroxychloroquine was not efficacious as early treatment for COVID-19 infections in RCTs with low to very low quality of evidence for all outcomes. More RCTs are needed to elucidate the efficacy of hydroxychloroquine as early treatment intervention.

Keywords: Hydroxychloroquine; COVID-19; efficacy; safety; early treatment
Introduction

Over 43 million people in the United States (US) have contracted COVID-19 resulting in ~698,000 deaths [1]. The surges in cases have brought with it over 3,000,000 hospitalizations that threaten to overwhelm the strained healthcare system [1]. One approach to reducing the impact of COVID-19 on the healthcare system is through early treatment of patients in the outpatient setting.

The monoclonal antibodies products bamlanivimab [2] and casirivimab/имевимаб [3] recently received emergency use authorization from the Food and Drug Administration (FDA) for the treatment of COVID-19 patients at high risk for progressing to hospitalization. While these early treatment trials were positive, bamlanivimab was found inefficacious for the treatment of hospitalized COVID-19 patients [4], supporting the hypothesis that antiviral therapy is most effective early in the course of disease [5].

The results of hydroxychloroquine randomized controlled trials (RCTs) and cohort studies for the treatment of hospitalized patients have been lackluster [6,7] and its emergency use authorization was revoked by the FDA [8]. However, at the November 2020 American Medical Association meeting, delegates tried to get the organization to revoke its statement discouraging the use of hydroxychloroquine for COVID-19, especially for the early outpatient treatment of the disease [9]. That same month, several panelists at a US Senate hearing touted hydroxychloroquine’s outpatient use in COVID-19, and asked for its emergency use authorization to be reinstated [10]. If hydroxychloroquine is effective and safe in the early treatment of COVID-19, it would be markedly less expensive than monoclonal antibody therapy and much more readily available to roll out to the general public. However, the use of hydroxychloroquine may have adverse events and shunting utilization to COVID-19 patients...
could cause shortages for those patients who need hydroxychloroquine for autoimmune diseases and malaria [11].

In this systematic review with meta-analyses, we assessed the efficacy and safety of hydroxychloroquine in early onset treatment of COVID-19 from all the available randomized controlled trials.

Methods

Data Sources and Searches

Three investigators (C.M.W., V.P., and A.V.H.) developed the search strategy, which was revised and approved by the other investigators. We searched the following databases from December 01, 2019 to September 14, 2021: PubMed-MEDLINE, EMBASE-OVID, Scopus, Web of Science, the Cochrane Library, bioRxiv (www.biorxiv.org), Preprints (www.preprints.org), Clinical Trials.gov, the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/en/), and the Chinese Clinical Trials Registry (www.chictr.org.cn). The PubMed search strategy is shown in the Supplemental file.

Study Selection

We included randomized controlled studies (RCTs) in any language reporting benefit or harm outcomes from use of hydroxychloroquine as early treatment (i.e. a few days from symptom onset to enrolment) in outpatients with mild to moderate reverse transcription-polymerase chain reaction (RT-PCR)-confirmed COVID-19. We excluded studies in hospitalized COVID-19 patients, even though patients had mild to moderate disease and/or early disease, studies of prophylaxis with hydroxychloroquine (i.e. in those without COVID-19 disease), and cohort
studies evaluating hydroxychloroquine as early treatment of COVID-19. Three investigators (A.V.H., V.P., Y.M.R.) independently screened each record title and abstract for potential inclusion. Three investigators (V.P., J.J.B., Y.M.R.) then read the full text of the records whose abstracts had been selected by at least one investigator. Discrepancies were resolved through discussion or by a fourth investigator (A.V.H.).

**Outcomes**

Primary outcomes were hospitalization and all-cause mortality. Secondary outcomes were intensive care unit (ICU) admission, need of mechanical ventilation, COVID-19 symptom resolution, viral clearance in nasopharyngeal swabs, adverse events, and specific adverse events (e.g. diarrhea, headache, QTc prolongation).

**Data Extraction**

Two investigators (A.P., J.J.B.) independently extracted the following variables from studies: study setting, country, mean age, proportion of male, time from symptom onset in days, proportion of chronic coexisting diseases, hydroxychloroquine dose and duration, type of control and description, additional drug interventions, primary and secondary outcomes, and time of follow up. Discrepancies were resolved through discussion or by a third investigator (A.V.H.).

**Risk of bias assessment**

Two investigators (A.P., J.J.B.) independently assessed risk of bias (RoB) of randomized controlled trials with the Cochrane Risk of Bias 2.0 tool for RCTs [12,13]; disagreements were resolved by discussion with a third investigator (A.V.H.). RoB 2 assesses five domains: bias due
to the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. RoB of each domain and each RCT was described as low, some concerns or high.

**Statistical analyses**

We reported our systematic review according to 2009 PRISMA guidelines [14]. Inverse variance random effect meta-analyses were performed to evaluate effect of hydroxychloroquine vs. control on outcomes when outcome data was available for at least two RCTs or cohorts judged to have homogeneous study characteristics. Effects of meta-analyses were reported as relative risks (RR) for dichotomous outcomes and as mean differences (MD) for continuous outcomes, along with their 95% confidence intervals (CIs). CIs of effects were adjusted with the Hartung-Knapp method [15], and the between study variance tau² was calculated with the Paule-Mandel method. Heterogeneity of effects among studies was quantified with the I² statistic (an I²>60% means high heterogeneity). The *meta* package of R 3.5.1 (www.r-project.org) was used for meta-analyses. The quality of evidence (QoE) was evaluated using the GRADE methodology, which covers five aspects: risk of bias, inconsistency, indirectness, imprecision, and publication bias [16]. Quality of evidence was evaluated per outcome and described in summary of findings (SoF) tables; GRADEpro GDT was used to create SoF tables [17].

**Results**

**Selection of studies**

Our comprehensive search yielded 9551 citations with an additional 927 citations identified through other sources, including backwards citation tracking. After removing duplicates and
applying our inclusion and exclusion criteria (Fig. S1), we identified five RCTs [18-22] (n=1848) which were all homogenous enough to warrant meta-analyses.

**Characteristics of included studies**

The general characteristics of the included RCTs are included in Table I. Placebo was the comparator in four RCTs [19-22] while usual care was the comparator in the open label one [18]. The five RCTs used hydroxychloroquine total doses between 1,600 and 4,400 mg and had follow up times between 14 and 90 days. Mean or median ages ranged between 37 and 53 years-old, males between 31% and 55%, median time of COVID-19 symptom onset between 3 and 7 days, with most of individuals within 9 days of symptom onset, and the proportion of individuals without coexisting disease between 36% and 68%.

**Risk of bias of included studies**

One RCT had high risk of bias due to missing outcome data [19], two RCTs had some concerns of bias due to deviations from intended interventions and selection in the reported result [18] and due to bias in the randomization process [21], and two RCTs had low risk of bias [20,22] (Fig. S2).

**Effects of early treatment with hydroxichloroquine on outcomes**

In comparison to the control group, hydroxychloroquine non-significantly reduced hospitalizations by 20% (RR 0.80, 95%CI 0.47-1.36, I²=2%, 5 RCTs, low QoE, Fig. 1) and all-cause mortality by 23% (RR 0.77, 95%CI 0.16-3.68, I²=0%, 5 RCTs, very low QoE, Fig. 2). Also, hydroxychloroquine had no effect on COVID-19 symptom resolution (RR 0.94, 95%CI...
0.77-1.16, I²=71%, 3 RCTs, low QoE, Fig. S3), time to COVID-19 symptom resolution (MD -
0.16 days, 95%CI -4.56 to 4.25 days, I²=80%, 2 RCTs, very low QoE, Fig. S4) and on viral
clearance at 14 days (RR 1.02, 95%CI 0.82-1.27, I²=65%, 2 RCTs, low QoE, Fig. S5) in
comparison to the control group.

There was no data about ICU admissions or need of mechanical ventilation in RCTs.
Hydroxychloroquine non-significantly increased risks of adverse events in comparison to the
control group (RR 2.17, 95%CI 0.86-5.45, I²=92%, 5 RCTs, very low QoE, Fig. 3). There was
very scarce report of specific adverse events in the RCTs.

Quality of evidence of effects
The quality of evidence was low to very low for all outcomes (Table II). The main drivers of
poor quality of evidence in RCTs were high risk of bias, imprecision of effects and
inconsistency.

Discussion
In our systematic review we found that hydroxychloroquine as early treatment for COVID-19
was not associated with lower hospitalization, all-cause mortality, or overall adverse events risks
vs. controls (usual care or placebo) in five RCTs. There was no effect of hydroxychloroquine on
COVID-19 symptom resolution or viral clearance at 14 days. No data on other outcomes such as
ICU admissions, need for mechanical ventilation, or specific adverse events was reported. The
quality evidence was low to very low in all outcomes.

The 20% relative reductions in hospitalizations in RCTs is encouraging, especially since
three of the biggest RCTs had the same direction of effect in favor of hydroxychloroquine but
none of the individual risks was significant across RCTs. If this were a real benefit of therapy, reducing relative risks of hospitalizations in those recently contracting COVID-19 by one fifth would make a difference in the overstressed healthcare system. However, more RCTs of higher methodologic quality are needed for us to adequately assess this outcome with the use of early treatment with hydroxychloroquine in the future.

The RCTs found no impact on all-cause mortality; probable reasons included scarcity of events (i.e. one event per arm in Skipper et al. [19] and one event in the control arm in Reis et al. [21]), and also short time of follow up as Skipper et al. [19] only had a 14-day, Mitjá et al. [18] and Johnston et al. [20] only had 28 days, and Schwartz et al. [22] only had 30 days, so it could have been too soon to see mortality reductions. The dose of hydroxychloroquine therapy was not a viable explanation for the lack of effect on all-cause mortality across RCTs as the total doses in the RCTs ranged from 3,200 mg to 4,400 mg, with the exception of the small RCT by Schwartz et al. [22] with 1,600 mg of total dose. The duration of hydroxychloroquine was not a viable explanation either with RCTs providing hydroxychloroquine therapy for 5 to 9 days. Three recent systematic reviews and meta-analyses including RCTs until October 16, 2020 did not evaluate mortality effects of hydroxychloroquine in outpatients [23-25]; two other recent systematic reviews and meta-analyses including RCTs until October 15, 2020 [26,27] only assessed mortality effects in COVID-19 outpatients using the Mitja et al. [18] and Skipper et al. [19] RCTs.

Hydroxychloroquine for the early treatment of COVID-19 would compete against the monoclonal antibody products bamlanivimab [2] and casirivimab/indevimab [3] that were recently received emergency use authorization from the FDA for the treatment of COVID-19 patients at high risk for progressing to hospitalization. These drugs will cost between $1,250 and
$1,500 per dose according to governmental contracts. Bamlanivimab was authorized based on the results from the ‘Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies’ (BLAZE-1) RCT [28]. In the combined bamlanivimab dosing group, the incidence of hospitalizations or emergency department visits was non-significantly lower (3 of 309 [1.6%] vs. 9 of 143 [6.3%]) by day 29. In a 799-patient trial that is still unpublished [29], treatment with casirivimab/indevimab was associated with a 57% reduction in COVID-19-related medical visits through day 29, which was significantly greater than the placebo group (p=0.024).

The National Institutes of Health COVID-19 Treatment Guideline Panel [2] has cautioned that there is insufficient evidence of bamlanivimab’s efficacy in early outpatient treatment and has not commented on the use of casirivimab/indevimab because the data is unpublished. As such, we cannot determine if any of these therapies is truly beneficial in the early treatment of COVID-19 or if one option is superior to the others. If hydroxychloroquine is subsequently found to significantly reduce hospitalizations, it would offer several advantages over monoclonal antibody therapy including better established safety profile, lower acquisition cost, more convenient dosing form, and more ample supply for COVID-19 patients.

However, if hydroxychloroquine is not truly efficacious or effective, the adverse events associated with therapy would not be balanced out with benefits and shunting the drug supply away from patients with autoimmune diseases could negatively impact other patients in the healthcare system. In a study of 3,872 patients taking hydroxychloroquine or chloroquine for autoimmune diseases [11], 27%, 21%, 7%, and 2% of patients in Africa, South-East Asia, North and South America and Europe, respectively, reported running out of medication due to drug shortages in the COVID-19 era. These patients experienced poorer physical (5.6 < 6.4, t(254) =
5.97, p<0.001) and mental (5.8 < 6.3, t(252) = 3.82, p<0.001) health and higher levels of rheumatic disease activity (5.1 > 4.3, t(244) = 4.44, p<0.001) as a result.

Our study has several limitations. First, all outcomes had low to very low quality of evidence mainly explained by heterogeneity of effects across trials, high risk of bias or some concerns of bias of three RCTs, and imprecision of effects. Second, there was very scarce all-mortality data across RCTs, and only two or three RCTs had information on symptom resolution or viral clearance. Third, there was no data on ICU admissions, need of mechanical ventilation, or specific adverse events. Fourth, four of the five RCTs [19-22] had fewer patients randomized than originally planned; this may have been resulted in lack of power to detect effects of hydroxychloroquine on outcomes. Finally, we did not evaluate the effect of adding azithromycin to hydroxychloroquine in our study.

Conclusion

Hydroxychloroquine as early treatment did not reduce hospitalizations, all-cause mortality, COVID-19 symptom resolution, and viral clearance in COVID-19 outpatients from five RCTs in comparison to placebo or usual care. There also was a non-significant increase in adverse events with hydroxychloroquine as early treatment. There was no data for outcomes such as ICU admission, need of mechanical ventilation or specific adverse events. The quality of evidence was low to very low for all outcomes.

Given its low acquisition cost, relative safety, convenient administration route, and available supply, hydroxychloroquine should continue to be investigated for outpatients who test positive for COVID-19. However, hydroxychloroquine should not be recommended for acute
treatment at this time because the balance of benefits to harms cannot be determined given the current literature base.

**Disclosure statement:** The authors declare no conflict of interest.

**References**


29. May B. Regeneron’s REGN-COV2 Cocktail Meets Clinical Endpoints in Phase II/III Trial. 10/30/2020. Available at: https://www.biospace.com/article/regeneron-s-regn-
Figure Legends

**Figure 1.** Effect of early treatment with HCQ on hospitalization.

**Figure 2:** Effect of early treatment with HCQ on all-cause mortality.

**Figure 3:** Effect of early treatment with HCQ on adverse events.
SUPPLEMENTAL FILE

Efficacy and effectiveness of early treatment with hydroxychloroquine in people with mild to moderate COVID-19: A systematic review and meta-analysis

Supplemental Methods: PubMed Search Strategy

Figure S1: Flowchart of study selection

Figure S2: Risk of bias assessment of randomized controlled trials

Figure S3: Effect of early treatment with HCQ on COVID-19 symptom resolution by 14 to 30 days.

Figure S4: Effect of early treatment with HCQ on time to COVID-19 symptom resolution in days.

Figure S5: Effect of early treatment with HCQ on viral clearance at 14 days.
PubMed Search strategy

("hydroxychloroquine"[MeSH Terms] OR "hydroxychloroquine"[All Fields] OR
("chloroquin"[All Fields] OR "chloroquine"[MeSH Terms] OR "chloroquine"[All Fields] OR
"chloroquine s"[All Fields] OR "chloroquines"[All Fields])) AND ("severe acute respiratory
syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome
coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR "covid
19"[All Fields] OR "sars cov 2"[All Fields] OR ("coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]) OR ("severe acute respiratory
syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome
coronavirus 2"[All Fields] OR "sars cov 2"[All Fields]))
Figure S1: Flowchart of study selection

Records identified through database searching (n = 9552)

Additional records identified through other sources (n = 927)

Records after duplicates removed (n = 6139)

Records screened (n = 6139)

Records excluded (n = 5962)

Full-text articles excluded, with reasons (n = 172)
- 22 cohorts of HCQ hospital treatment
- 10 RCTs of HCQ hospital treatment
- 132 uncontrolled studies of HCQ hospital treatment
- 5 HCQ prophylaxis studies
- 3 HCQ early treatment cohorts

Full-text articles assessed for eligibility (n = 177)

Studies included in qualitative synthesis (n = 5)

Studies included in quantitative synthesis (meta-analysis) (n = 5)
Figure S2: Risk of bias assessment of randomized controlled trials

As percentage (intention-to-treat)

- Overall Bias
- Selection of the reported result
- Measurement of the outcome
- Missing outcome data
- Deviations from intended interventions
- Randomization process

Legend:
- Low risk
- Some concerns
- High risk
**Figure S3:** Effect of early treatment with HCQ on COVID-19 symptom resolution by 14 to 30 days.

<table>
<thead>
<tr>
<th>Source</th>
<th>Hydroxychloroquine</th>
<th>Control</th>
<th>RR [95%-CI]</th>
<th>Favors Control</th>
<th>Favors HCQ</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skipper 2020</td>
<td>152</td>
<td>135</td>
<td>1.09 [0.96; 1.23]</td>
<td></td>
<td></td>
<td>45.0%</td>
</tr>
<tr>
<td>Johnston 2021</td>
<td>30</td>
<td>38</td>
<td>0.95 [0.68; 1.32]</td>
<td></td>
<td></td>
<td>22.4%</td>
</tr>
<tr>
<td>Schwartz 2021</td>
<td>67</td>
<td>29</td>
<td>0.77 [0.61; 0.97]</td>
<td></td>
<td></td>
<td>32.6%</td>
</tr>
<tr>
<td><strong>Random effects model</strong></td>
<td><strong>249</strong></td>
<td><strong>202</strong></td>
<td><strong>0.94 [0.77; 1.16]</strong></td>
<td></td>
<td></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 71\%$, $\tau^2 = 0.0210$, $p = 0.03$
Figure S4: Effect of early treatment with HCQ on time to COVID-19 symptom resolution in days.

<table>
<thead>
<tr>
<th>Source</th>
<th>Hydroxychloroquine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Milja 2020</td>
<td>10.50</td>
<td>10.4000</td>
</tr>
<tr>
<td>Schwartz 2021</td>
<td>14.50</td>
<td>7.4000</td>
</tr>
</tbody>
</table>

Random effects model: 225

Heterogeneity: $I^2 = 80\%$, $\tau^2 = 8.0668$, $p = 0.03$
Figure S5: Effect of early treatment with HCQ on viral clearance at 14 days.

<table>
<thead>
<tr>
<th>Source</th>
<th>Hydroxychloroquine</th>
<th>Control</th>
<th>RR [95%-CI]</th>
<th>Favors Control</th>
<th>Favors HCQ</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnston 2021</td>
<td>43 49</td>
<td>40 52</td>
<td>1.14 [0.95; 1.37]</td>
<td>Black</td>
<td>Blue</td>
<td>50.1%</td>
</tr>
<tr>
<td>Reis 2021</td>
<td>97 185</td>
<td>112 195</td>
<td>0.91 [0.76; 1.10]</td>
<td>Black</td>
<td>Red</td>
<td>49.9%</td>
</tr>
<tr>
<td>Random effects model</td>
<td>140 234</td>
<td>152 247</td>
<td>1.02 [0.82; 1.27]</td>
<td>Black</td>
<td>Red</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 65\%$, $x^2 = 0.0162$, $p = 0.09$
# PRISMA 2009 Checklist

<table>
<thead>
<tr>
<th>Section/topic</th>
<th>#</th>
<th>Checklist item</th>
<th>Reported on page #</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TITLE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
<td>1</td>
</tr>
<tr>
<td><strong>ABSTRACT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structured summary</td>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria; participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
<td>2</td>
</tr>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
<td>3</td>
</tr>
<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
<td>3-4</td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol and registration</td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
<td>NA</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
<td>4-5</td>
</tr>
<tr>
<td>Information sources</td>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
<td>4</td>
</tr>
<tr>
<td>Search</td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
<td>4, Supplement</td>
</tr>
<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
<td>4-5</td>
</tr>
<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
<td>5</td>
</tr>
<tr>
<td>Data items</td>
<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
<td>5</td>
</tr>
<tr>
<td>Risk of bias in individual studies</td>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
<td>5-6</td>
</tr>
<tr>
<td>Summary measures</td>
<td>13</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
<td>6</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>14</td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.</td>
<td>6</td>
</tr>
<tr>
<td>Section/topic</td>
<td>#</td>
<td>Checklist item</td>
<td>Reported on page #</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>----</td>
<td>-------------------------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
<td>6</td>
</tr>
<tr>
<td>Additional analyses</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
<td>NA</td>
</tr>
<tr>
<td>RESULTS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study selection</td>
<td>17</td>
<td>Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.</td>
<td>6-7, Fig S1</td>
</tr>
<tr>
<td>Study characteristics</td>
<td>18</td>
<td>For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.</td>
<td>7, Table 1</td>
</tr>
<tr>
<td>Risk of bias within studies</td>
<td>19</td>
<td>Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).</td>
<td>7, Fig S2</td>
</tr>
<tr>
<td>Results of individual studies</td>
<td>20</td>
<td>For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.</td>
<td>7, Figs 1 to 3, Figs S3 to S5</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>21</td>
<td>Present results of each meta-analysis done, including confidence intervals and measures of consistency.</td>
<td>7-8, Figs 1 to 3, Figs S3 to S5</td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>22</td>
<td>Present results of any assessment of risk of bias across studies (see Item 15).</td>
<td>7, Fig S2</td>
</tr>
<tr>
<td>Additional analysis</td>
<td>23</td>
<td>Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).</td>
<td>NA</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary of evidence</td>
<td>24</td>
<td>Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).</td>
<td>8-10</td>
</tr>
<tr>
<td>Limitations</td>
<td>25</td>
<td>Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).</td>
<td>11</td>
</tr>
<tr>
<td>Conclusions</td>
<td>26</td>
<td>Provide a general interpretation of the results in the context of other evidence, and implications for future research.</td>
<td>11-12</td>
</tr>
<tr>
<td>FUNDING</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funding</td>
<td>27</td>
<td>Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.</td>
<td>12</td>
</tr>
</tbody>
</table>
PRISMA 2009 Checklist


For more information, visit: www.prisma-statement.org.

Page 2 of 2
<table>
<thead>
<tr>
<th>Source</th>
<th>Hydroxychloroquine Events</th>
<th>Total Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>RR [95% CI]</th>
<th>Favors HCQ</th>
<th>Favors Control</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milja 2020</td>
<td>8</td>
<td>136</td>
<td>11</td>
<td>157</td>
<td>0.84 [0.35; 2.03]</td>
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<td>34.2%</td>
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<tr>
<td>Skipper 2020</td>
<td>4</td>
<td>212</td>
<td>10</td>
<td>211</td>
<td>0.40 [0.13; 1.29]</td>
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<td>20.7%</td>
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<tr>
<td>Johnston 2021</td>
<td>4</td>
<td>71</td>
<td>2</td>
<td>83</td>
<td>2.34 [0.46; 12.39]</td>
<td></td>
<td></td>
<td>9.9%</td>
</tr>
<tr>
<td>Rels 2021</td>
<td>8</td>
<td>214</td>
<td>11</td>
<td>227</td>
<td>0.77 [0.32; 1.88]</td>
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<td>33.4%</td>
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<tr>
<td>Schwartz 2021</td>
<td>4</td>
<td>110</td>
<td>0</td>
<td>37</td>
<td>6.35 [0.12; 343.57]</td>
<td></td>
<td></td>
<td>1.8%</td>
</tr>
</tbody>
</table>

Random effects model 28 743 34 715 0.80 [0.47; 1.36] 100.0%

Heterogeneity: $\hat{\tau}^2 = 0.0108$, $I^2 = 0$%

Fig 1 hospitalization R1
Fig 2 all-cause mortality R1
<table>
<thead>
<tr>
<th>Source</th>
<th>Hydroxychloroquine Events</th>
<th>Hydroxychloroquine Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>RR [95%-CI]</th>
<th>Favors HCQ</th>
<th>Favors Control</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitja 2020</td>
<td>121</td>
<td>169</td>
<td>16</td>
<td>184</td>
<td>8.23 [5.11; 13.28]</td>
<td>25.5%</td>
<td></td>
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<tr>
<td>Skipper 2020</td>
<td>92</td>
<td>212</td>
<td>46</td>
<td>211</td>
<td>1.99 [1.48; 2.68]</td>
<td>26.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnston 2021</td>
<td>3</td>
<td>71</td>
<td>5</td>
<td>83</td>
<td>0.70 [0.17; 2.83]</td>
<td>16.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reis 2021</td>
<td>46</td>
<td>214</td>
<td>46</td>
<td>227</td>
<td>1.06 [0.74; 1.53]</td>
<td>26.3%</td>
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<td></td>
</tr>
<tr>
<td>Schwartz 2021</td>
<td>5</td>
<td>91</td>
<td>0</td>
<td>33</td>
<td>7.81 [0.16; 373.15]</td>
<td>4.7%</td>
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<td></td>
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<tr>
<td><strong>Random effects model</strong></td>
<td><strong>267</strong></td>
<td><strong>757</strong></td>
<td><strong>113</strong></td>
<td><strong>738</strong></td>
<td><strong>2.17 [0.86; 5.45]</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 92\%$, $\chi^2 = 0.8045$, $p < 0.01$

Fig 3 adverse events R1