Hydroxychloroquine in COVID-19: A systematic review and meta-analysis

Jose Chacko[1], Gagan Brar[2], Robert Premkumar[1]

[1]Department of Critical Care Medicine, Majumdar Shaw Medical Center, Bangalore, India
[2]Department of Critical Care Medicine, Aster RV Hospital, Bangalore, India

Corresponding Author:

Jose Chacko, MD DNB EDIC
Majumdar Shaw Medical Center
Bangalore, India
Email: jose.chacko.dr01@narayanahealth.org

Running Title: Hydroxychloroquine in COVID-19

Hydroxychloroquine in COVID-19: A systematic review and meta-analysis

Abstract

Background

Hydroxychloroquine is being administered among patients with COVID-19 infection in many healthcare systems across the world considering its in vitro effect against the SARS-CoV-2 virus. In spite of several observational studies and a few randomized controlled trials, the effect of hydroxychloroquine on patients with COVID-19 infection remains unclear. We undertook this systematic review with meta-analysis to evaluate the efficacy and safety of hydroxychloroquine among patients with COVID-19 infection.

Methods

We searched PubMed, Embase, the Cochrane Library, Web of Science, medRxiv, and other relevant resources until May 13, 2020. We included randomized controlled trials and observational studies in which hydroxychloroquine was adminstered and compared to a control group. Data were extracted, and quality assessment of the studies was carried out. We evaluated symptomatic progression, mortality, viral clearance, the evolution of changes on chest CT imaging, and adverse events. A fixed or random-effects model was used depending on outcome heterogeneity.

Results

We included eleven studies including, three randomized controlled trials and eight observational studies. Among these, 2354 patients received hydroxychloroquine alone or in combination, while 1952 did not. Mortality was reported at different points of time. The overall mortality was not significantly different among patients who received hydroxychloroquine compared to the control group (OR: 1.41, 95% CI: 0.76–2.62; p = 0.28). Clinical worsening or lack of symptomatic improvement did not differ between patients who received hydroxychloroquine compared to those who did not (OR 1.1, 95% CI: 0.6–2.02; p = 0.76). Viral clearance, assessed by RT-PCR, did not differ significantly between the hydroxychloroquine and the control groups (OR: 1.13, CI: 0.26–5.01; p = 0.87). The evolution of changes on chest CT imaging was reported only in two studies; a more pronounced improvement was observed with the use of hydroxychloroquine compared to standard care (OR: 2.68, CI: 1.1–6.6; P = 0.03). The incidence of adverse events was significantly higher with hydroxychloroquine (OR: 4.1, CI: 1.42–11.88; p = 0.009).

Conclusions

Our meta-analysis does not suggest improvement in clinical progression, mortality, or viral clearance by RT-PCR among patients with COVID-19 infection who are treated with hydroxychloroquine. There was a significantly higher incidence of adverse events with hydroxychloroquine use.

Keywords

COVID-19, SARS-COV-2, hydroxychloroquine, meta-analysis

Introduction

Late last year, a novel coronavirus outbreak was identified in Wuhan, China. The SARS-CoV-2 virus spread exponentially across the globe, and the World Health Organization declared it as a pandemic in March 2020 (1). The treatment of COVID-19 infection remains largely supportive; several treatment modalities have been proposed including the aminoquinolines, chloroquine and hydroxychloroquine. Both these drugs have been extensively used to treat malaria, systemic lupus erythematosus, and rheumatoid arthritis. There has been increasing interest in the possible efficacy of these agents in COVID-19 infection, considering their anti-inflammatory and antiviral effects in vitro (2). The Food and Drug Administration in the US authorized emergency use of these drugs in the treatment of COVID-19 infection in March 2020, followed by extensive use across the world (3). Hydroxychloroquine has a more potent antiviral effect and may be safer compared to chloroquine (4) and hence is more commonly used in clinical practice. Following an early report from Marseilles, France (5), which revealed more rapid viral clearance, there has been increasing interest in the efficacy of hydroxychloroquine in COVID-19 infection. However, many of these studies are limited by the lack of a control arm and are inadequate to draw definitive conclusions (6,7).

The clinical efficacy of hydroxychloroquine in patients with COVID-19 infection remains unclear despite numerous studies of limited sample size. A meta-analysis of small studies could reduce the possibility of a type II error by increasing the sample size, and may reveal any possible benefit from the intervention. Hence, we performed a systematic review and meta-analysis of available controlled studies to evaluate the safety and efficacy of hydroxychloroquine in the treatment of COVID-19 infection.

Methods

Search strategy and study selection

The meta-analysis was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We performed a systematic search of PubMed, Embase, the Cochrane Library, Web of Science, and the medRxiv databases until May 13, 2020. Besides, we performed gray literature search using online search engines, blog search, and hand search through the table of contents of key journals. We used the keywords “COVID-19”, “SARS-CoV-2”, and “hydroxychloroquine” to search for articles. Boolean operators (AND, OR, NOT) were used as appropriate to identify relevant literature. No filters were set for the search process.

We evaluated the titles and abstracts of articles for potential study inclusion. Furthermore, the bibliography of the selected articles and previous systematic reviews were assessed for relevant articles.

Inclusion and exclusion criteria

Studies were considered eligible if they included patients who received hydroxychloroquine alone or in combination with other specific treatment modalities for COVID-19 infection and were compared with a control group. Both randomized controlled trials (RCTs) and observational studies with a comparator group were considered for inclusion. Data on at least one of the following outcomes had to be available for inclusion in the meta-analysis: (i) mortality, (ii) clinical progress, (iii) results of the reverse transcription-polymerase chain reaction (RT-PCR) test after the commencement of treatment, (iv) changes on computed tomography (CT) imaging of the chest, and (iv) adverse clinical events. We excluded studies in languages other than English and those with incomplete data.

Data extraction, assessment of study quality, and risk of bias

Data were collected independently by two authors. We collected data on the name of the first author, year of publication, study design, location of the study, the number of patients included in each group, and the dose of hydroxychloroquine administered. The outcomes evaluated included clinical worsening or non-improvement, mortality at any point in time, improvement of lesions on chest CT imaging, and adverse events. The Cochrane risk of bias tool was used to evaluate RCTs. The ROBINS-I tool was used to assess the risk of bias in observational studies. Disagreement between investigators was resolved through discussion and consensus.

Statistical analysis

The outcomes studied were dichotomous; point estimates are expressed as odds ratio (OR) with the 95% confidence interval (CI). Heterogeneity of outcomes was calculated using the I^2 statistic. An I^2 value of 0%–40% was considered to be not important; 30% to 60% as moderate heterogeneity; 50%–90 as substantial heterogeneity and 75% to 100% as considerable heterogeneity (8). We used a random-effects model for $I^2 \geq 40\%$ and a fixed-effects model for $I^2 < 40\%$. The meta-analysis was performed using the Mantel Hazel method as all the endpoints were dichotomous. A p-value < 0.05 was considered to be statistically significant. All analyses were performed using Review Manager 5.3 (RevMan 5.3; The Cochrane Collaboration, Oxford, UK).

Funding source

We had no funding source for the conduct of this meta-analysis.

Results

Selection of studies

We identified 434 publications through database searching. An additional article was obtained through hand searching. We evaluated the title and abstract of 408 articles after removing 27 duplicate publications. Of these, 373 records were excluded as they were not relevant to the meta-analysis. The full text of 35 publications was evaluated in detail; 24 of these were excluded. The excluded articles comprised of 11 review articles, nine letters,

editorials or opinion, and three non-clinical studies. One of the studies was excluded, as it had no control arm (6). The flow chart of study selection is depicted in Figure 1.

Characteristics, quality, and risk of bias assessment of the included studies

The main characteristics of the studies included in the meta-analysis are presented in Table 1. Three were RCTs and the remaining eight were observational studies. The included studies comprised of a total of 4306 patients; 2354 were in hydroxychloroquine arm, while 1952 were in the control group.

The risk of bias among the included RCTs, assessed by the Cochrane risk of bias tool, is presented in Figure 2. Among the observational studies, three were considered to be at low risk (9–11), four at moderate risk (10–13), and one at a high risk of bias (5).

Outcomes

Six studies provided data on mortality, assessed at variable time points. Hospital mortality was reported by three studies (9,13,14). Among the other three, one study reported mortality at 7 days (15), while another reported 5-day mortality (12). Geleris et al. studied patients from March 7 to April 8, 2020, with follow-up until April 25, 2020. The overall mortality was 468 of 2190 (21.4%) with hydroxychloroquine vs. 385 of 1804 (21.3%) in the control arm (11). Significant statistical heterogeneity was observed between studies in the evaluation of mortality ($I^2 = 84\%$); hence we used a random-effects model for analysis. Mortality was not significantly different among patients who received hydroxychloroquine compared to those who did not (OR: 1.41, 95% CI: 0.76–2.62; p = 0.28); (Figure 3)

Clinical worsening was reported as an outcome in three studies (16–18). In the RCT by Zhaowei et al., with 31 patients each in the hydroxychloroquine and control arms, worsening of pneumonia was observed in 4 of 31 (12.9%) patients in the control group compared to none in the hydroxychloroquine group (16). In another RCT, Tang et al. reported no symptomatic improvement with hydroxychloroquine in 30 of 75 (40%) patients compared to 25 of 75 (33.3%) patients who received standard care (17). Heterogeneity between studies in the assessment of clinical progression was minimal ($I^2 = 39\%$); hence we analyzed the results using a fixed-effects model. Clinical worsening or lack of symptomatic improvement did not differ between patients who received hydroxychloroquine compared to those who received standard care alone (OR 1.1, 95% CI: 0.6–2.02; p = 0.76) (Figure 4).

Viral clearance by RT-PCR was reported at different time points in four studies (5,10,17,18). Two studies reported on negative conversion of RT-PCR by 7 days (5,18), while the other two studies reported at 14 and 28 days (10,17). There was substantial heterogeneity between studies ($I^2 = 65\%$); hence we used a random-effects model in the evaluation of this outcome. Negative conversion rate by RT-PCR was not significantly different between the hydroxychloroquine and control groups (OR: 1.13, CI: 0.26–5.01; p = 0.87) (Figure 5).

We evaluated the improvement in changes on CT imaging of the chest, as reported in two studies (16,18). There was no heterogeneity noted between studies ($I^2 = 0$). A more pronounced improvement on the repeat CT scan was observed with the use of hydroxychloroquine compared to standard care (OR: 2.68, CI: 1.1–6.6; P = 0.03) (Figure 6).

Adverse events were reported in four studies (14,16–18). Two studies reported on the number of patients who developed adverse events (16,18), while one study reported on the total number of adverse events in each group (17). Rosenberg et al. reported cardiac arrest and abnormal ECG findings (14). There was substantial heterogeneity between studies (I^2 =81%); hence we used a random-effects model. Adverse events were significantly more common with hydroxychloroquine compared to the control group (OR: 4.1, CI: 1.42–11.88; p = 0.009) (Figure 7).

Sensitivity analysis

Considering that there were only three RCTs in the included studies, it was feasible to perform sensitivity analysis only for viral clearance by RT-PCR. We performed sensitivity analysis for RT-PCR negativity based solely on two RCTs that reported viral clearance, excluding observational studies by Gautret et al. (5) and Mallat et al. (10). On sensitivity analysis, there was no significant difference in the negative conversion rate by RT-PCR between patients who received hydroxychloroquine compared to those who did not (OR: 1.18, CI: 0.53–2.66; p = 0.68) (Figure 8).

Discussion

The synthesized evidence from our meta-analysis suggests that the use of hydroxychloroquine in patients with COVID-19 infection does not result in more rapid relief of symptoms, or improve mortality. Besides, hydroxychloroquine does not appear to lead to a more rapid viral clearance by RT-PCR. Exposure to hydroxychloroquine resulted in a higher incidence of adverse events compared to patients who did not receive hydroxychloroquine.

Chloroquine and its congener, hydroxychloroquine, have revealed anti-inflammatory and antiviral effects in vitro, with the latter exhibiting more potent activity (19). Hydroxychloroquine exerts its antiviral effect by increasing endosomal pH within the cells (20). Besides, it inhibits glycosylation of receptors on the cell surface, which prevents binding of the SARS-CoV-2 virus to the ACE-II receptor (21). This results in blockade of the entry pathway of the virus into the cell. Since the outbreak of the pandemic in China in late last year, there has been an upsurge of interest on the clinical efficacy of hydroxychloroquine in COVID-19 infection.

In an early study from Marseilles, France, 20 patients with confirmed COVID-19 disease received hydroxychloroquine 600 mg/d; azithromycin was added based on the clinical situation. Sixteen patients from another center acted as controls. By day 3, 50% of hydroxychloroquine-treated patients tested negative for the virus by RT-PCR compared to 6.3% in the control group; by day 6, 70% among the treated group tested negative compared to 12.5% in the control group. The addition of azithromycin seemed to augment viral clearance (5). However, the outcomes of six patients from the treatment group were not reported in this study. Clinical worsening occurred in three patients requiring ICU admission, and one patient died, while treatment was discontinued in two other patients. Three other studies evaluated the time to viral clearance by RT-PCR. These studies tested RT-PCR at different points in time; Chen et al. reported no difference in viral clearance rates on the 7th day of treatment (18). Tang et al., in their RCT, found no difference in the primary endpoint of the rate of RT-PCR negativity at 28 days with hydroxychloroquine treatment (17). RT-PCR negativity was also comparable at days 4,7,10, and 14 days in this study. In the Mallat et al. study, RT-PCR negativity was significantly lower with hydroxychloroquine compared to

the control group (10). Our meta-analysis also revealed no effect of hydroxychloroquine on viral clearance by RT-PCR testing with the administration of hydroxychloroquine. The in vitro antiviral effect of hydroxychloroquine against the SARS-CoV-2 virus needs validation in clinical practice.

Mortality as a clinical outcome was addressed in six observational studies. In the study by Geleris et al., mortality at the time of study follow-up was higher in the hydroxychloroquine group compared to controls. No significant association was observed with the use of hydroxychloroquine and intubation or death (11). Magagnoli et al. categorized patients into those who received hydroxychloroquine alone, and in combination with azithromycin, and compared them with patients who did not receive hydroxychloroquine. All-cause hospital mortality was significantly higher among patients who received hydroxychloroquine alone compared to those who did not (13). In two other studies, no difference was observed in the 5- and 7-day mortality with the use of hydroxychloroquine (12,15). Only one study reported lower hospital mortality with the use of hydroxychloroquine compared to standard care (9). The study by Rosenberg et al. had four patients categories, including those who received hydroxychloroquine alone, in combination with azithromycin, azithromycin alone, and those who received neither drug. Treatment with hydroxychloroquine was associated with a significantly higher mortality compared to those who did not (OR: 2.49; CI: 1.79–3.46) (14). The findings of our meta-analysis also support the absence of a mortality benefit with the use of hydroxychloroquine in COVID-19 infection.

The impact of hydroxychloroquine on symptomatic progression was assessed by three studies. Two studies were of small sample size, with very few patients who experienced worsening of symptoms in either group (16,18). The study by Zhaowei et al. assessed “time to clinical recovery”, which included resolution of fever and cough; other relevant outcomes, including organ dysfunction, were not considered (16). In the study by Tang et al., there was no significant difference in symptomatic improvement between patients who underwent hydroxychloroquine treatment compared to those who did not (17). Overall, hydroxychloroquine administration did not have a significant impact on symptomatic progression.

The effect of hydroxychloroquine on chest CT imaging was assessed in two studies (16,18). Both studies showed improved resolution of consolidation. However, these studies included a small number of patients, making the findings difficult to interpret.

It is important to note that the dose of hydroxychloroquine used varied between studies, ranging from 400–1200 mg/day. A dose of more than 800 daily has been predicted to rapidly decrease viral loads compared to a dose of 400 mg daily or less based on in vitro and pharmacokinetic data; however, at higher doses, complications including prolongation of the QT-interval may occur, leading to adverse clinical outcomes (22). The optimal dose of hydroxychloroquine for clinically important antiviral effects remains unknown and needs further research.

The combination of hydroxychloroquine with azithromycin was reported in six studies (5,11,13–15,17). However, the number of patients who received this combination was small and precluded meaningful analysis. It remains unclear whether this combination may be more efficacious compared to hydroxychloroquine alone. Besides, both hydroxychloroquine and azithromycin carry the risk of QT prolongation and sudden cardiac death when used in

combination (23). Future studies are required to address the possible benefit of this combination in COVID-19 infection.

Two previous meta-analyses have been performed to assess the efficacy of hydroxychloroquine among patients with COVID-19 infection (24,25). However, each of these meta-analyses included only three controlled studies with a limited number of patients, and no definitive conclusions could be drawn. In contrast, the present meta-analysis included eleven controlled studies, including a much larger number of patients.

Our meta-analysis is limited by the heterogeneous nature of the studies included. We included both RCTs and observational studies, which may limit the robustness of outcome assessment. The baseline severity of illness also varied between studies. Most of the studies were of small sample size, and underpowered to evaluate the outcomes that were addressed. The endpoints, including mortality, clinical progress, and viral clearance by RT-PCR, were reported at variable points of time, making it difficult to interpret. The dose of hydroxychloroquine used varied between studies. We did not assess the possible effect of using azithromycin in combination with hydroxychloroquine, considering the small number of patients who received both drugs.

In conclusion, our meta-analysis does not support the treatment of COVID-19 infection with hydroxychloroquine. We did not observe a significant difference in mortality, the progression of symptoms, or viral clearance on RT-PCR with hydroxychloroquine administration. Resolution of consolidation on chest CT seems to occur more rapidly with hydroxychloroquine, although the impact on clinical outcomes remains unclear. Adverse events were significantly more with the use of hydroxychloroquine. Adequately powered RCTs are required to evaluate the possible efficacy of hydroxychloroquine in CVOID-19 infection, the optimal dosage, and additive effects when combined with azithromycin.

References

1. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [Internet]. [cited 2020 May 13]. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020

2. Devaux CA, Rolain J-M, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int J Antimicrob Agents. 2020 Mar 12;105938.

3. Sandler, R. (2020, April 6). FDA Authorizes anti-malarial drugs chloroquine and hydroxychloroquine For emergency coronavirus treatment. Retrieved from https://www.forbes.com/sites/rachelsandler/2020/03/30/fda-approves-anti-malarial-drugs-chloroquine-and-hydroxychloroquine-for-emergency-coronavirus-treatment/.

4. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis Off Publ Infect Dis Soc Am. 2020 Mar 9;

5. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020 Mar 20;105949.

6. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Sevestre J, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. Travel Med Infect Dis. 2020 Apr 11;101663.

7. Million M, Lagier J-C, Gautret P, Colson P, Fournier P-E, Amrane S, et al. Full-length title: Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. Travel Med Infect Dis. 2020 May 5;101738.

8. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557–60.

9. Yu B, Wang DW, Li C. Hydroxychloroquine application is associated with a decreased mortality in critically ill patients with COVID-19 [Internet]. Emergency Medicine; 2020 May [cited 2020 May 7]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.04.27.20073379

10. Mallat J, Hamed F, Balkis M, Mohamed MA, Mooty M, Malik A, et al. Hydroxychloroquine is associated with slower viral clearance in clinical COVID-19 patients with mild to moderate disease: A retrospective study [Internet]. Infectious Diseases (except HIV/AIDS); 2020 May [cited 2020 May 7]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.04.27.20082180

11. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020 May 7;NEJMoa2012410.

12. Barbosa et al. Clinical outcomes of hydroxychloroquine in hospitalized patients with COVID-19: A quasi-randomized comparative study. Submitted to the New England Journal of Medicine. (April 11th 2020).

13. Magagnoli J, Narendran S, Pereira F, Cummings T, Hardin JW, Sutton SS, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19 [Internet]. Infectious Diseases (except HIV/AIDS); 2020 Apr [cited 2020 May 7]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.04.16.20065920

14. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. JAMA [Internet]. 2020 May 11 [cited 2020 May 13]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2766117

15. Mahevas M, Tran V-T, Roumier M, Chabrol A, Paule R, Guillaud C, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial [Internet]. Infectious Diseases (except HIV/AIDS); 2020 Apr

[cited 2020 May 7]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.04.10.20060699

16. Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial [Internet]. Epidemiology; 2020 Mar [cited 2020 May 7]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.03.22.20040758

17. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial [Internet]. Infectious Diseases (except HIV/AIDS); 2020 Apr [cited 2020 May 7]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.04.10.20060558

18. Chen et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ (Med Sci) 2020, Vol. 49 Issue (1): 0-0 DOI: 10.3785/j.issn.1008-9292.2020.03.03.

19. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;6:16.

20. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis Off Publ Infect Dis Soc Am. 2020 Mar 9;

21. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005 Aug 22;2:69.

22. Garcia-Cremades M, Solans BP, Hughes E, Ernest JP, Wallender E, Aweeka F, et al. Optimizing hydroxychloroquine dosing for patients with COVID-19: An integrative modeling approach for effective drug repurposing. Clin Pharmacol Ther [Internet]. 2020 Apr 14 [cited 2020 May 12]; Available from: http://doi.wiley.com/10.1002/cpt.1856

23. Pires dos Santos R, Kuchenbecker R. Azithromycin and the risk of cardiovascular death. N Engl J Med. 2012 23;367(8):774–5; author reply 775.

24. Sarma P, Kaur H, Kumar H, Mahendru D, Avti P, Bhattacharyya A, et al. Virological and clinical cure in COVID-19 patients treated with hydroxychloroquine: A systematic review and meta-analysis. J Med Virol. 2020 May 3;jmv.25898.

25. Shamshirian A, Hessami A, Heydari K, Alizadeh-Navaei R, Ebrahimzadeh MA, Yip GW, et al. Hydroxychloroquine Versus COVID-19: A Rapid Systematic Review and MetAnalysis. medRxiv. 2020 May 10;2020.04.14.20065276.

Table 1. Summary of characteristics of the studies included in the meta-analysis. HCQ, hydroxychloroquine; azi, azithromycin

Study	Country	Design	Intervention	Control	Outcomes
Chen et al.	China	RCT	HCQ 400 mg/d x 5 d	Standard treatment	RT-PCR negativity on d 7, Clinical worsening, CT changes, adverse events
Tang et al.	China	RCT	HCQ 200 mg/d x 3 d followed by 800/d	Standard treatment	RT-PCR negativity on d 28, clinical progression, adverse events
Zhaowei et al.	China	RCT	HCQ 400 mg/d x 5 d	Standard treatment. Included oxygen therapy, antivirals, antibiotics, immunoglobulin, corticosteroids	Time to clinical recovery, CT changes
Barbosa et al.	US	Observational	HCQ 400 mg twice daily x 1–2 d; 200–400 mg/d x 3–4 d	Usual care	Mortality at 5 d, escalation of respiratory support
Gautret et al.	France	Observational	HCQ 200 mg thrice daily; azi 500 mg/d x 1d, 250 mg/d x 4 d in 6 patients	Details not available	RT-PCR negativity d 6
Geleris et al.	US	Observational	HCQ 600 mg twice daily x 1d; 400 mg	Standard treatment	Mortality until study follow-up

			daily for 4 days. Azi 500 mg x 1d; 250 mg/d x 4 d as option. Left to physician judgement.		date. Composite of intubation or mortality on time-to-event analysis.
Magagnoli et al.	US	Observational	HCQ alone or in combination with azi. Details of dosing not available	Standard treatment	Hospital mortality, need for mechanical ventilation
Mahevas et al.	France	Observational	HCQ 600 mg/d	Standard treatment	Mortality at 7 d, need for ICU care, development of ARDS[
Mallat et al.	Abu Dhabi	Observational	HCQ 400 mg twice daily x 1 d, followed by 400 mg daily x 10 days.	Standard treatment	RT-PCR negativity d 14
Rosenberg et al.	US	Observational	HCQ 200 mg–400 mg once or twice daily	4 groups: HCQ alone, HCQ+azi, azi alone, and neither	Hospital mortality, cardiac arrest, abnormal ECG findings
Yu et al.	China	Observational	HCQ 200 mg twice a day x 7–10 d	Standard treatment	Hospital mortality

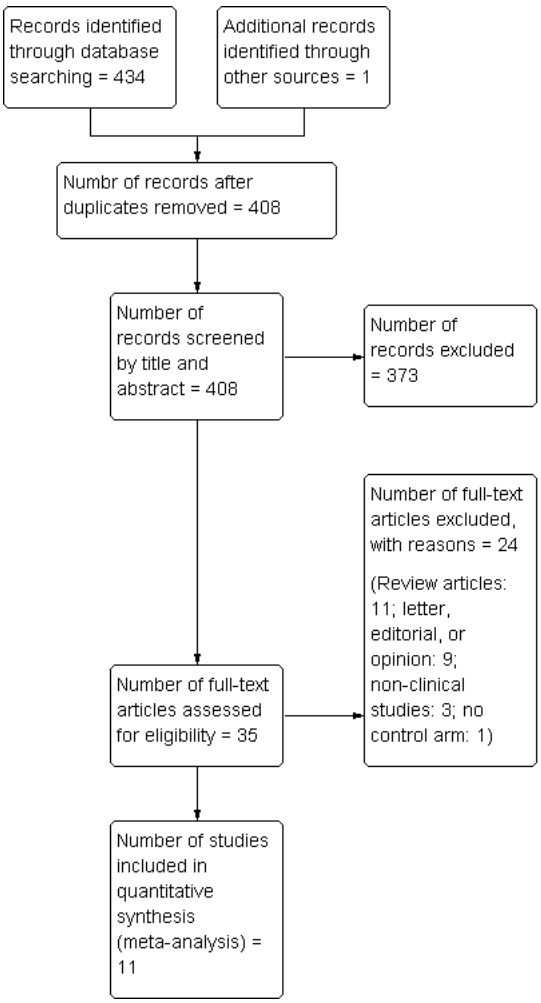

Figure 1. Flow diagram depicting the process of selection of the included studies

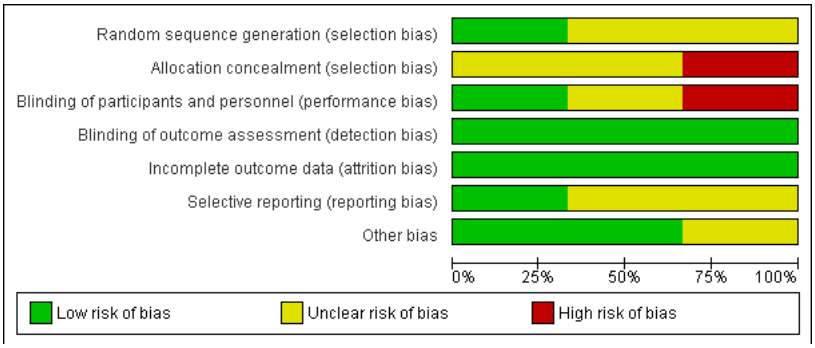

Figure 2. Risk-of-bias graph of randomized controlled studies using the Cochrane tool

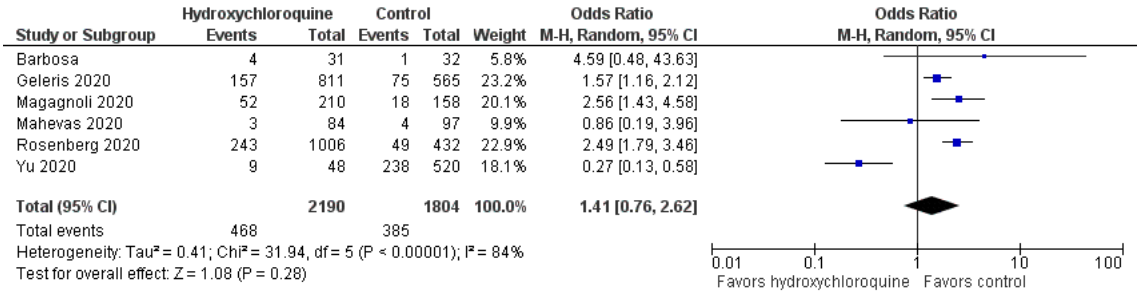

Figure 3. Forest plot comparing mortality between the hydroxychloroquine and the control groups. CI, confidence interval; df, degrees of freedom; M-H, Mantel–Haenszel; Random, random-effects model.

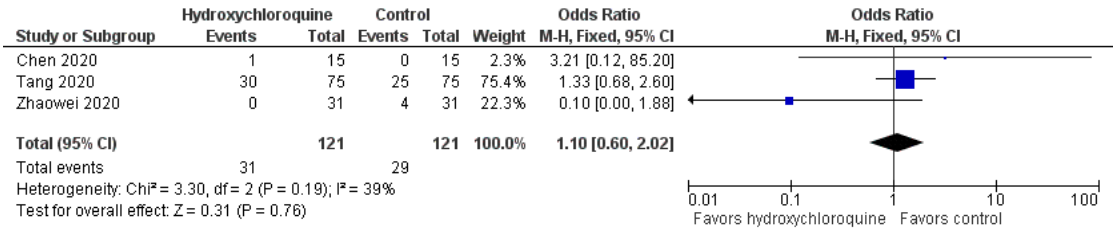

Figure 4. Forest plot comparing clinical worsening between the hydroxychloroquine and the control groups. CI, confidence interval; df, degrees of freedom; M-H, Mantel–Haenszel; Fixed, fixed-effects model

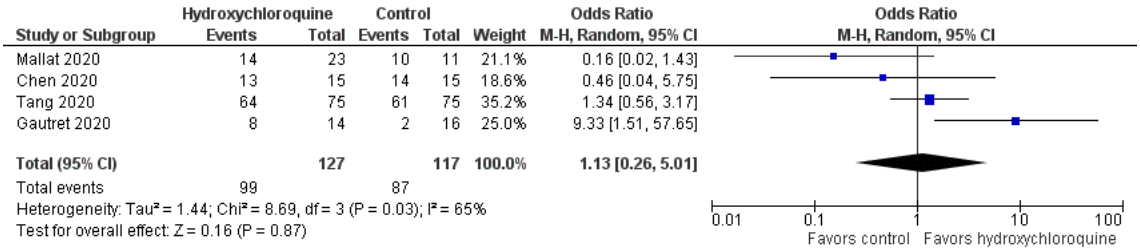

Figure 5. Forest plot comparing viral clearance by RT-PCR between the hydroxychloroquine and the control groups. CI, confidence interval; df, degrees of freedom; M-H, Mantel–Haenszel; Random, random-effects model

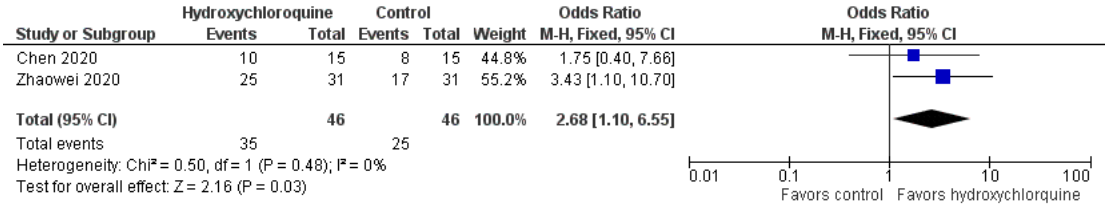

Figure 6. Forest plot comparing resolution of changes on CT chest between the hydroxychloroquine and the control groups. CI, confidence interval; df, degrees of freedom; M-H, Mantel–Haenszel; Fixed, fixed-effects model

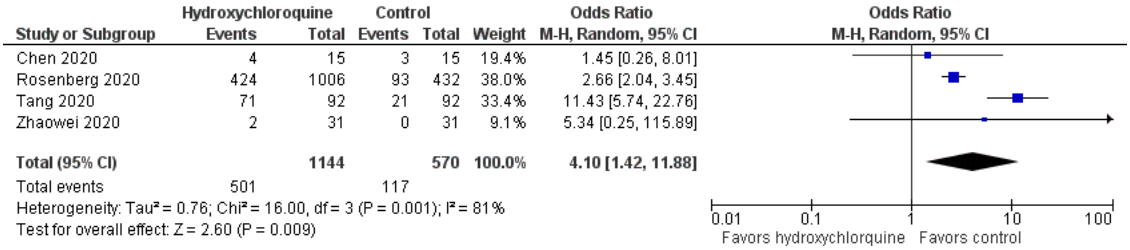

Figure 7. Forest plot comparing adverse events between the hydroxychloroquine and the control groups. CI, confidence interval; df, degrees of freedom; M-H, Mantel–Haenszel; Random, random-effects model

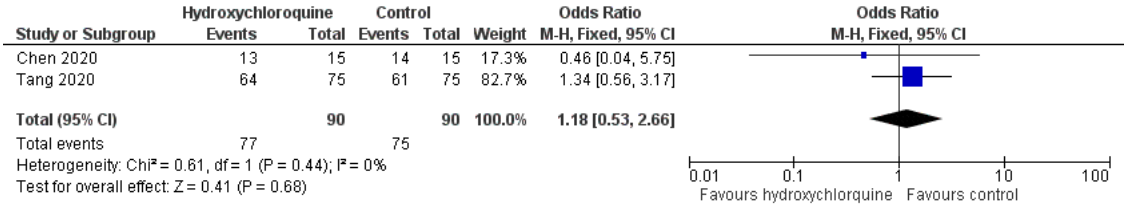

Figure 8. Forest plot comparing viral clearance by RT-PCR in two randomized controlled trials