PATHOGENS AND GLOBAL HEALTH
2021, VOL. 115, NO. 3, 139–150
https://doi.org/10.1080/20477724.2021.1884807

Taylor & Francis
Taylor & Francis Group

Use of hydroxychloroquine and chloroquine in patients with COVID-19: a meta-analysis of randomized clinical trials

Paulo Roberto Bignardi[a], Carolina Santos Vengrus[a], Bruno Matos Aquino[a] and Alcindo Cerci Neto[a,b]

[a]School of Medicine, Pontifical Catholic University of Paraná, Londrina, Brazil; [b]Section of Pulmonology, Department of Medicine, Health Science Centre, State, University of Londrina, Londrina, Brazil

ABSTRACT

COVID-19 has quickly become a public health problem worldwide, and treatment for this new disease is needed. Hydroxychloroquine is an antimalarial that *in vitro* studies have shown action against SARS-CoV-2, which is why it has been the target of clinical studies with conflicting results. Therefore, the aim of this systematic review was to assess the association of hydroxychloroquine use with the virological cure, clinical recovery, mortality, and development of adverse effects in patients with COVID-19. PubMed, Cochrane Library, and Lilacs were searched until 7 January 2021, for randomized clinical trials with COVID-19 patients treated with hydroxychloroquine or chloroquine. Of the 130 studies found, 12 met the inclusion criteria. Compared to the patient's control group, the risk ratio (RR) for the virological cure and clinical recovery with hydroxychloroquine or chloroquine use was 1.04 (95%CI 0.91–1.17) and 1.03 (95%CI 0.92–1.13), respectively. Hydroxychloroquine (with or without azithromycin) was also not associated with mortality (RR = 1.09, 95%CI 0.98–1.20). Treatment with hydroxychloroquine was associated with any adverse effects (RR = 1.50, 95%CI 1.18–1.81). Hydroxychloroquine or chloroquine use did not have a significant effect on virological cure, the time of clinical recovery, and improvement in survival in COVID-19 patients. However, patients who used hydroxychloroquine showed an increase in adverse effects.

KEYWORDS

Chloroquine; coronavirus; hydroxychloroquine; meta-analysis; SARS-CoV-2

Introduction

On 31 December 2019, the World Health Organization's China Country Office was informed by local authorities of pneumonia deaths of unknown etiology in Wuhan, Hubei Province of China [1]. After a few weeks, the causative agent was identified as a new coronavirus (SARS-CoV-2) and the disease called COVID-19 [2,3]. In less than 3 months, on 11 March 2020, the World Health Organization (WHO) declared the COVID-19 as a pandemic disease [4].

Increased mortality and the fast spread of the disease worldwide have made the scientific community engage in a global effort to find the best treatment for COVID-19. Chloroquine (CQ) and Hydroxychloroquine (HCQ), drugs that belong to the quinolone family and are used to prevent and treat malaria, showed effectiveness against SARS-CoV-2 in the first *in vitro* studies [5,6]. Two initial small clinical trials reported a decrease in the viral load and better clinical recovery with high doses of HCQ use in patients with COVID-19 [7,8]. Following these results, other observational studies have found unclear results on the beneficial use of HCQ/CQ in any disease phase.

Recent randomized clinical trials have not shown better outcomes in patients treated with these drugs. There is much controversy about using this treatment worldwide, and some advocate that these drugs could be helpful at the beginning of the disease in the viral phase. Therefore, considering the contrast of conclusions, we decided to perform a systematic review and meta-analysis of data involving the administration of CQ and HCQ in patients with COVID-19 and virological cure, clinical recovery, mortality, adverse effects, need for mechanical ventilation, and hospital discharge.

Methods

Research strategy

This study is a systematic review of randomized clinical trials. We conducted a review of the databases: PubMed, Lilacs, and Cochrane Library. Studies published until 7 January 2021, were included. The following keywords were used as search terms: 'coronavirus', 'coronavirus disease', 'COVID-19', 'treatment', 'hydroxychloroquine', 'chloroquine', 'clinical trial'. The references for all selected articles were also retrieved and, due to the urgency of publications related to COVID-19, additional references were searched manually on the MedRxiv prepress server.

CONTACT Paulo Roberto Bignardi pbignardi@gmail.com School of Medicine, Pontifical Catholic University of Paraná, 485 Jockey Club Ave - Vila Hípica, Londrina, Paraná 86072-360, Brazil

Studies selection

Two independent authors screened this review. Disagreements were solved through discussion among all authors. Titles and abstracts of retrieved articles were revised to exclude irrelevant studies, followed by screening. Clinical trials were included when they met the following inclusion criteria: (1) COVID-19 patients using HCQ or CQ; (2) patients who did not use HCQ or CQ as a comparison group; (3) randomized controlled trial; (4) examination of the relationship between HCQ or CQ use and time to negative viral nucleic acid test, time to clinical recovery, mortality, adverse effects, use of mechanical ventilation (MV), hospital discharges, or kidney and thromboembolic complications. The study was conducted in accordance with the Preferred Items guidelines for Reporting for Systematic Reviews and Meta-Analysis (PRISMA), and this study has not been registered.

Data Extraction

Data extraction was performed by two independent authors according to a data collection form. Possible conflicts were discussed with all authors. The information extracted includes authors, year of publication, study design, country of origin, population characteristics (age and sample size), type of treatment, disease severity, duration of follow-up, and measurement of effects for the researched outcomes. They should provide odds ratio (OR), ratio risk (RR), or hazard ratio (HR) with 95% confidence intervals (CI). Inclusion was not restricted by study size.

Quality Assessment

Two authors independently assessed the quality of the studies according to the Cochrane guidelines [9]. The following five domains were assessed: (1) bias arising from the randomization process; (2) bias due to deviations from the intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome; (5) bias in selection of the reported result. Any disagreements were resolved through discussion with a third author.

Results Assessment

The primary analysis focused on the outcomes: (1) time for negative detection of the viral nucleic acid; (2) time for clinical recovery; (3) mortality of the treated group in comparison to the control group.

The secondary analysis focused on the effect of treatment on the emergence of adverse effects, the use of MV, hospital discharge, renal and thromboembolic complications.

We performed a stratified analysis by type of treatment: HCQ only, CQ, and HCQ with azithromycin. In addition, a sensitivity analysis was performed when necessary omitting each study to detect the influence on the estimate of the overall effect.

Statistical Analysis

Studies included in the meta-analysis reported RR, OR, or HR. For studies that did not report these measures of effects, the RR calculation was based on the Cochrane Handbook for Systematic Reviews [10]. For studies that reported OR, a corrected RR was computed as already described [11]. HR was considered comparable to RR.

Pooled RR and 95% confidence interval (CI) were calculated using a fixed or random effects model according to the homogeneity of the studies. The Cochran's Q test and the I^2 statistic were used to evaluate the statistical significance and degree of heterogeneity between the studies, respectively. The result of $p \leq 0.05$ for the Q test represents statistical significance, and the statistic $I^2 \geq 50\%$ reveals substantial heterogeneity. Finally, the publication bias will be examined by the Egger test. All analyses were performed with Stata/SE v.14.1 software (StataCorpLP, USA).

Results

Study Selection and Characteristics of Included Studies

The initial search identified one hundred and thirty studies. Of these, 49 were excluded because they were duplicated. Inconsistent trials, non-clinical trials, non-therapeutic, and non-randomized studies were excluded. Of the remaining studies, 12 met the inclusion criteria and were selected for qualitative analysis, and eleven studies were included for the meta-analysis (Figure 1), totaling 7,629 patients. The investigated therapies found were as follows: HCQ in 10 studies, one study investigated HCQ only and HCQ plus azithromycin, and one study CQ therapy. One trial [12] investigated the effect of HCQ on individuals exposed to someone with confirmed COVID-19. The basic characteristics of the studies are shown in Table 1.

Effect of HCQ and CQ Therapy negating the viral nucleic acid test

The data were extracted and pooled from four studies. Three trials [13–15] studied HCQ only therapy versus usual care, and one trial [16] studied CQ therapy versus lopinavir/ritonavir combination. All trials used throat swab SARS-CoV-2 real-time reverse transcription-polymerase chain reaction (RT-PCR) nucleic acid at the beginning of the study to confirm COVID-19 and at the end to confirm the virological cure.

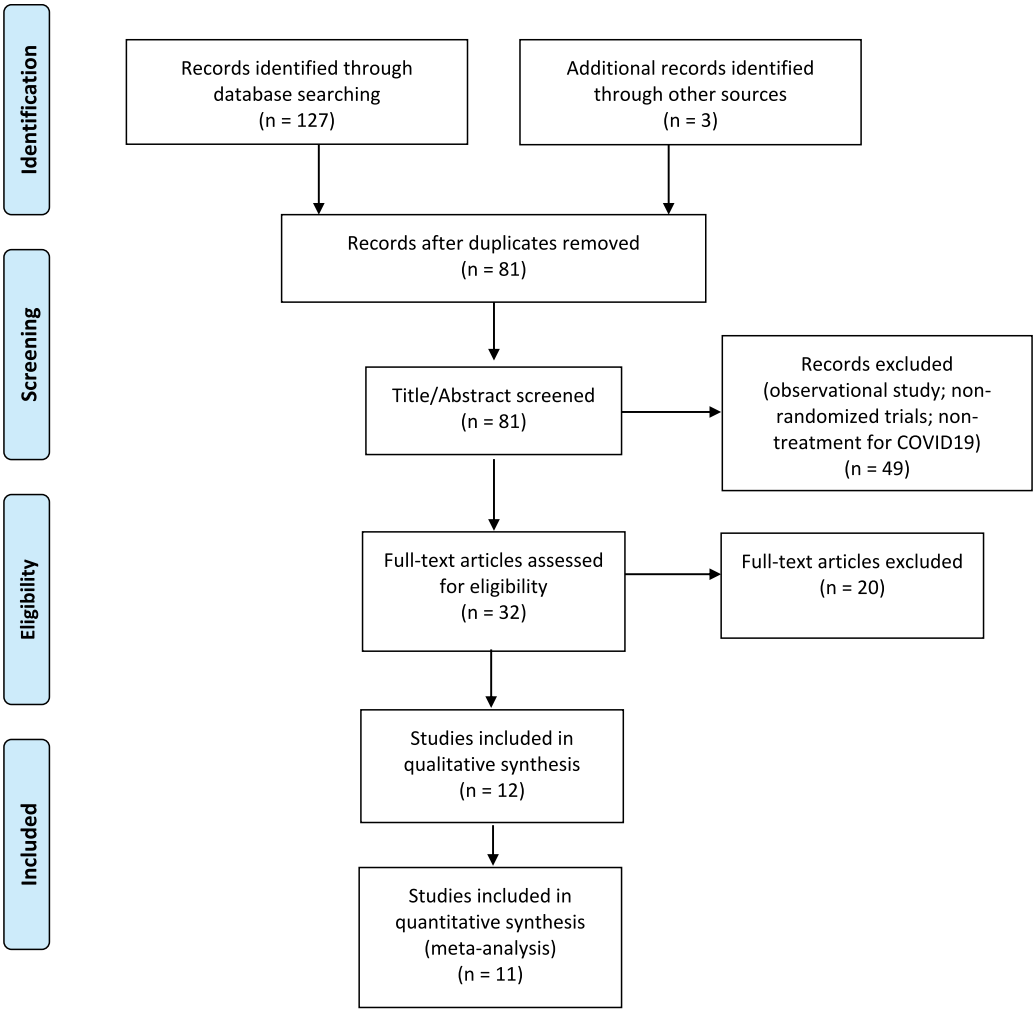

Figure 1. Flow chart of study selection.

Comparing the HCQ group with the control group, the results suggested no significant change in time for the virological cure (RR = 0.96, 95%CI 0.74–1.18). Combined with CQ study results, there was also no change in time for the negative RT-PCR (RR = 1.04, 95%CI 0.91–1.17, $P > 0.05$) (Figure 2).

Effect of HCQ and CQ only therapy in clinical recovery

The data were extracted from six studies that showed no decrease in time for clinical recovery in patients in the treated groups. Five trials [7,14,15,17,18] studied HCQ only therapy versus usual care, and one trial [16] studied CQ therapy versus lopinavir/ritonavir combination.

Combining the six studies, there was also no decrease in the time for clinical recovery (RR = 1.03, 95%CI 0.92–1.13, $P > 0.05$) (Figure 3).

Effect of HCQ only and HCQ plus azithromycin therapy in mortality

Cavalcanti et al. [19] studied treatments with HCQ only and HCQ plus azithromycin, while Abd-Elsalam et al. [17], Horby et al. [20], Lyngbakken et al. [21], and Self et al. 2020 [18] studied the treatment with HCQ only. The risk estimate for HCQ only was not different from the control group (RR = 1.09, 95%CI 0.98–1.20, $P > 0.05$). When HCQ with azithromycin was included, the result was similar without statistically significant differences (RR = 1.08, 95% CI 0.97–1.20, $P > 0.05$) (Figure 4).

Effect of CQ, HCQ only, and HCQ plus azithromycin therapy in any adverse effects

The data were extracted from seven studies. Five trials (11,17) studied HCQ only versus usual care, one trial [19] HCQ only versus usual care and HCQ plus azithromycin therapy versus usual care, and one trial [16] studied CQ therapy versus lopinavir/ritonavir combination. In the first analysis, the treatment with HCQ showed an increased risk of adverse effects (RR = 1.50, 95%CI 1.18–1.81, $P < 0.05$) compared to the control group. The analysis of all therapies also showed a significant increase in any adverse effects (RR = 1.44, 95%CI 1.21–1.68, $P < 0.05$) (Figure 5).

Table 1. Characteristics of the selected studies.

Author	Year	Country	Study Design	Drugs	Population	Outcomes	Sample Size	Age	Treatment Group (n)	Control (n)	Follow up
Abd-Elsalam et al	2020 t	Egypt	Randomized controlled trial.	Hydroxychloroquine 400 mg twice daily (in day 1) followed by 200 mg tablets twice daily *Vs* standard care	Hospitalized patients with confirmed COVID-19	Mechanical ventilation and clinical recovery	175	All Population 40.72 ± 19.32 HCQ group 40.35 ± 18.65 Control group 41.09 ± 20.07	97	97	28 days
Boulware et al	2020	USA and Canada	Randomized, double-blind, placebo-controlled trial	Hydroxychloroquine (800 mg once, followed by 600 mg for 4 days) *Vs* placebo	Adults exposed to confirmed covid-19 patients	Risk of infection, risk of hospitalization or death, severity of symptoms	821	HCQ group 41 (33–51)* Placebo group 40 (32–50)*	414	407	14 days
Cavalcanti et al.	2020	Brazil	Multicenter, randomized, open-label, three-group, controlled trial	Hydroxychloroquine (400 mg twice daily) or hydroxychloroquine (400 mg twice daily) plus azithromycin (500 mg once daily) *Vs* standard care	Hospitalized patients with suspected or confirmed Covid-19	Survival, adverse effects, need mechanical ventilation, kidney and thromboembolic complications	665	50.3 ± 16.6	HCQ group 221 HCQ + Azi group 217	227	15 days
Chen Jun et al.	2020	China	Randomized controlled trial.	Hydroxychloroquine (400 mg twice daily) *Vs* standard care	Patients with confirmed COVID-19	Time for negative RT-PCR, and adverse effects.	30	HCQ 50,5 ± 3,8 Control group 46,7 ± 3,6	15	15	7 days
Chen Cheng et al	2020	Taiwan	Randomized controlled trial.	Hydroxychloroquine (400 mg followed by 200 mg) *Vs* standard care	Adults patients with confirmed COVID-19	Negative RT-PCR, and clinical recovery	33	All Population 32.9 ± 10.7 HCQ group 33.0 ± 12 Control group 32.8 ± 8.3	21	12	14 days
Horby et al. (RECOVERY Group)	2020	UK	Multicenter, randomized, open-label, controlled trial	Hydroxychloroquine (800 mg followed by 400 mg) *Vs* usual care	Hospitalized patients with confirmed COVID-19	Death, time to discharge from hospital, mechanical ventilation, adverse effects	4716	HCQ group 65.2 ± 15.2 Control group = 65.4 ± 15.4	1561	3155	28 days
Huang et al.	2020	China	Randomized, open-label, controlled trial	Chloroquine (500 mg twice daily) Vs lopinavir/ritonavir (400/100 mg twice daily)	Hospitalized patients with confirmed covid-19	Time to negative RT-PCR, clinical recovery and time of hospital discharge	22	All Population 44.0 (36.5–57.5)* CQ group 41.5 (33.8–50.0)* Control group 53.0 (41.8–63.5)*	10	12 Lopinavir/ Ritonavir	10 days
Lyngbakken et al.	2020	Norway	Randomized, open-label, controlled trial	Hydroxychloroquine (400 mg twice daily) *Vs* standard care	Hospitalized patients with confirmed covid-19	SARS-CoV-2 viral load, adverse events, mortality at 30 days, and clinical status	53	All Population 62.0 (50–73)* HCQ group 56.0 (41–72)* Control group 69.0 (51–74)*	27	26	30 days

(*Continued*)

Table 1. (Continued).

Author	Year	Country	Study Design	Drugs	Population	Outcomes	Sample Size	Age	Treatment Group (n)	Control (n)	Follow up
Self et al	2020	USA	Multicenter, blinded, placebo-controlled randomized trial	Hydroxychloroquine (400 mg twice daily for 2 doses, then 200 mg twice daily for 8 doses) *Vs* placebo	Adults hospitalized with confirmed COVID-19	Clinical status and mortality	479	HCQ group 58 (45–69)* Control group 57 (43–68)*	242	237	28 days
Skipper et al	2020	USA	Randomized, double-blind, placebo-controlled trial	Hydroxychloroquine (800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 more days) *Vs* placebo	Symptomatic, non-hospitalized adults with laboratory- confirmed COVID-19 or probable COVID-19 and high-risk expo- sure within 4 days of symptom onset.	Severity disease and adverse events	423	HCQ group 41 (33–49)* Control group 39 (31–50)*	212	211	14 days
Tang et al.	2020	China	Multicenter, open label randomized controlled trial.	Hydroxychloroquine (1,200 mg daily for three days followed by 800 mg) *Vs* standard care	Hospitalized patients with confirmed COVID-19	Time to negative RT-PCR, clinical recover and adverse events of treatment	150	All Population 46.1 ± 14.7 HCQ group 48.0 ± 14.1 Control group 44.1 ± 15.0	75	75	23 days
Zhaowei Chen et al.	2020	China	Randomized clinical trial	Hydroxychloroquine (400 mg daily) *Vs* standard care	Patients with confirmed COVID-19	Time to clinical recover	62	All population 44,7 ± 15,3 HCQ group = 44,1 ± 16,1 Control group 45,2 ± 14,7	31	31	24 days

COVID-19, coronavirus disease; CQ, chloroquine; HCQ, hydroxychloroquine; HCQ+Azi, hydroxychloroquine plus azithromycin;
*data represented by median (IQR). Other age data represented by the mean (SD).

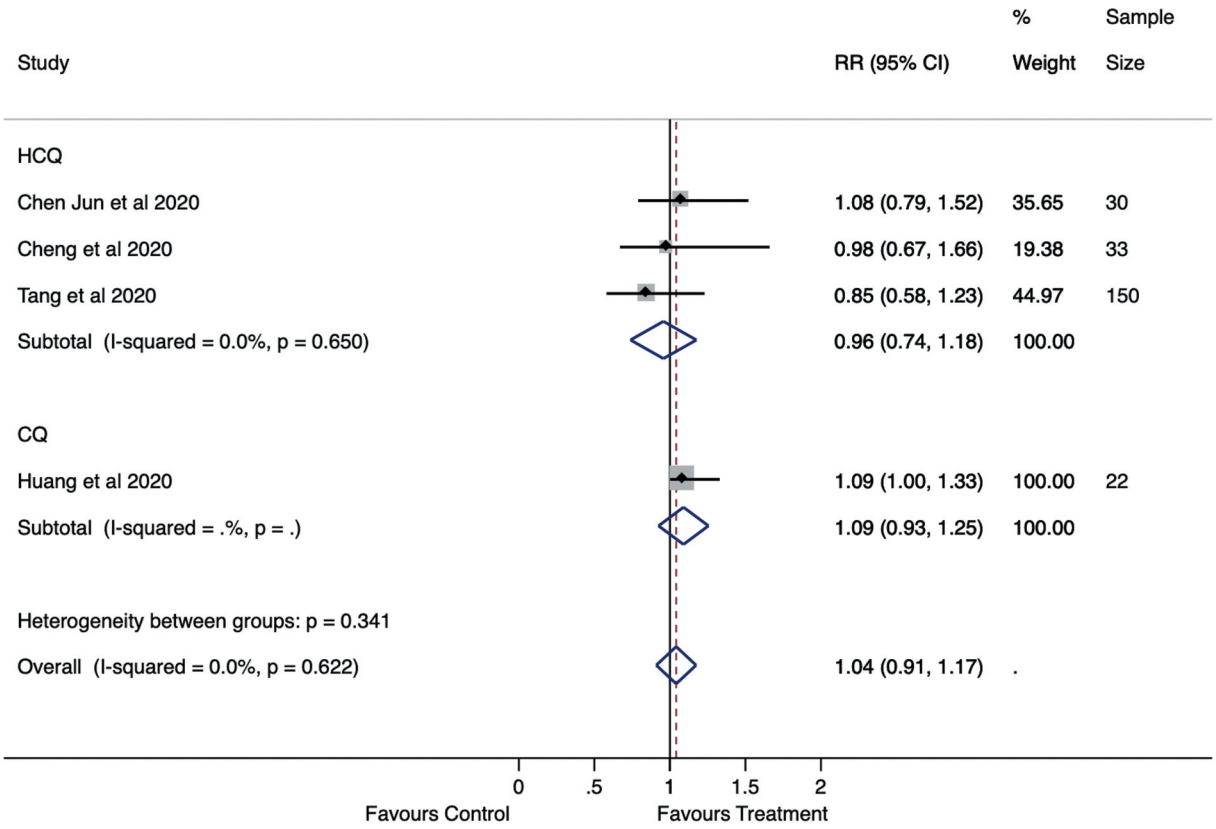

Figure 2. Effect of HCQ and CQ use on time for negative viral nucleic acid test. HCQ, hydroxychloroquine; CQ, chloroquine.

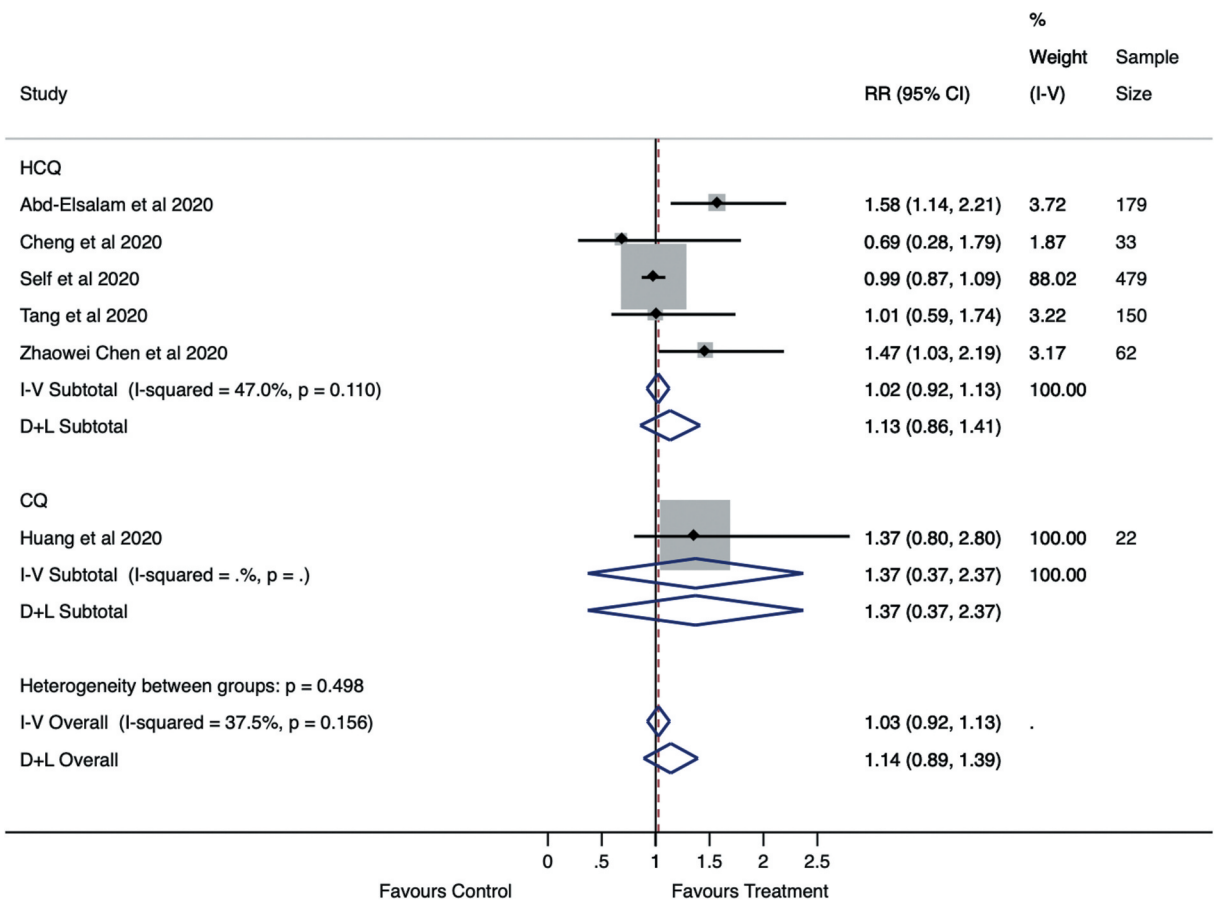

Figure 3. Effect of HCQ and CQ Use on Clinical Recovery. HCQ, hydroxychloroquine; CQ, chloroquine.

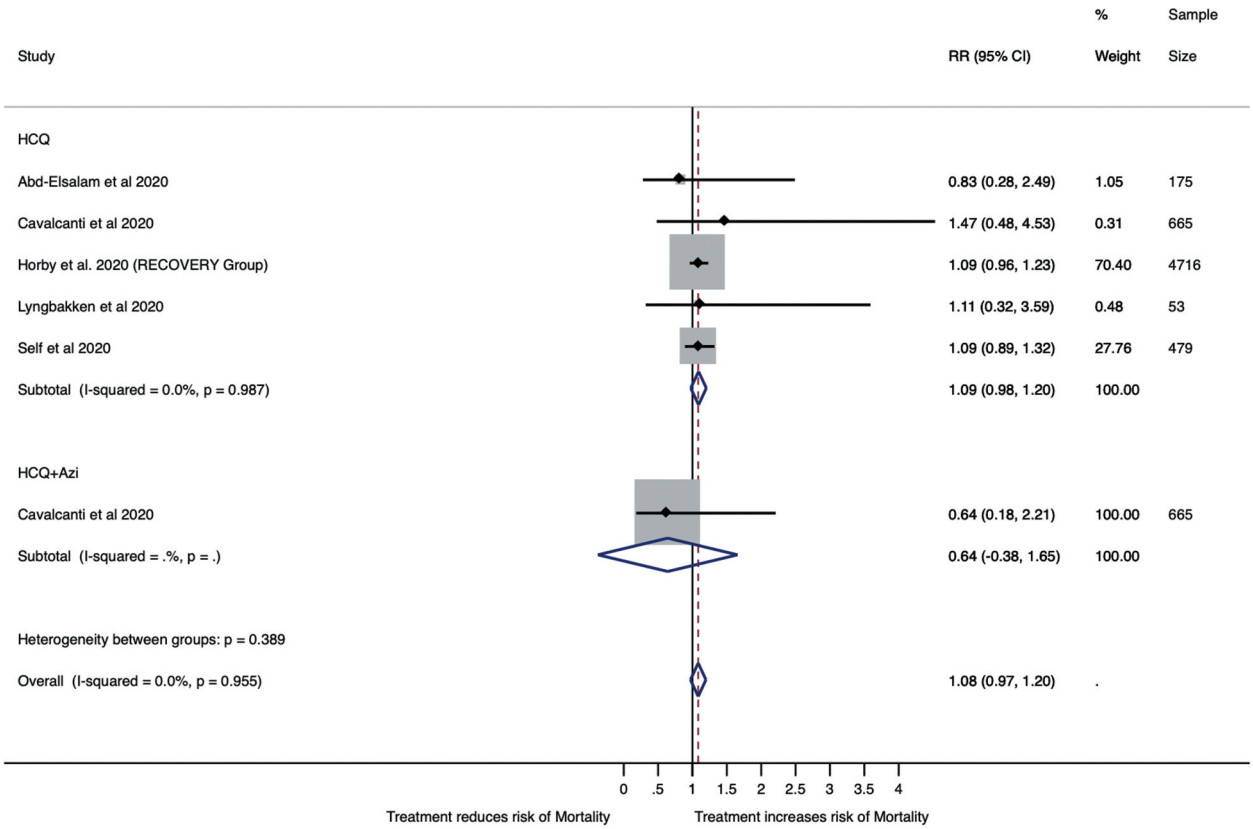

Figure 4. Effect of HCQ and HCQ+Azithromycin use on Mortality Risk. HCQ, hydroxychloroquine; HCQ, hydroxychloroquine plus azithromycin.

Effect of the therapies in other outcomes

The need to use MV was extracted from three trials [17,19,20]. Analysis of the HCQ only treatment showed no difference when compared to the control group (RR = 1.15, 95%CI 0.92–1.38, $P > 0.05$). Analysis including the HCQ plus azithromycin treatment also showed no difference with the control group (RR = 1.17, 95%CI 0.94–1.40, $P > 0.05$) (Figure 6).

Hospital discharge analysis was extracted from three trials. Two trials [18,20] studied HCQ therapy versus usual care and one trial [16] CQ versus lopinavir/ritonavir combination. The analysis revealed that HCQ treatment did not favor the hospital discharge (RR = 0.97, 95%CI 0.74–1.20, $P > 0.05$). Combined analysis of HCQ and CQ showed no difference when compared to the control group, but with substantial heterogeneity (RR = 1.05, 95%CI 0.73–1.38, $P > 0.05$, $I^2 = 54.6\%$) (Figure 7).

Renal and thromboembolic complications were described by Cavalcanti et al. [19], but with no differences between the control group and treatment group.

Sensitive analysis and publication bias

The heterogeneity of adverse effects analyses and clinical recovery was investigated by sensitivity analyses. Sensitivity analyses showed that excluding one study at a time from the analysis did not change the findings (Table 2).

For hospital discharges, the exclusion of Horby et al. [20] from the analysis changed the heterogeneity from substantial to moderate (I2 = 54.6% to 27.2%), yet did not alter the results.

The results of the estimated bias coefficient were from −0.177 to 0.195, giving a P-value > 0.05 for all analyses. Therefore, the tests provide weak evidence for the presence of publication bias.

Quality assessment of selected studies for meta-analysis

Among the studies selected for the meta-analysis, four trials [18–21] were considered as low risk of bias, five [7,14–16,22] as some concerns, and two [13,17] as high risk of bias. Two trials were randomized, double-blind, placebo-controlled trial, and nine trials were randomized, open-label, controlled study. The quality assessments of the studies included in the meta-analysis are shown in Figure 8.

Discussion

Despite all the controversy about HCQ and CQ use for COVID-19 treatment, this meta-analysis did not show any better outcomes in patients using HCQ or CQ

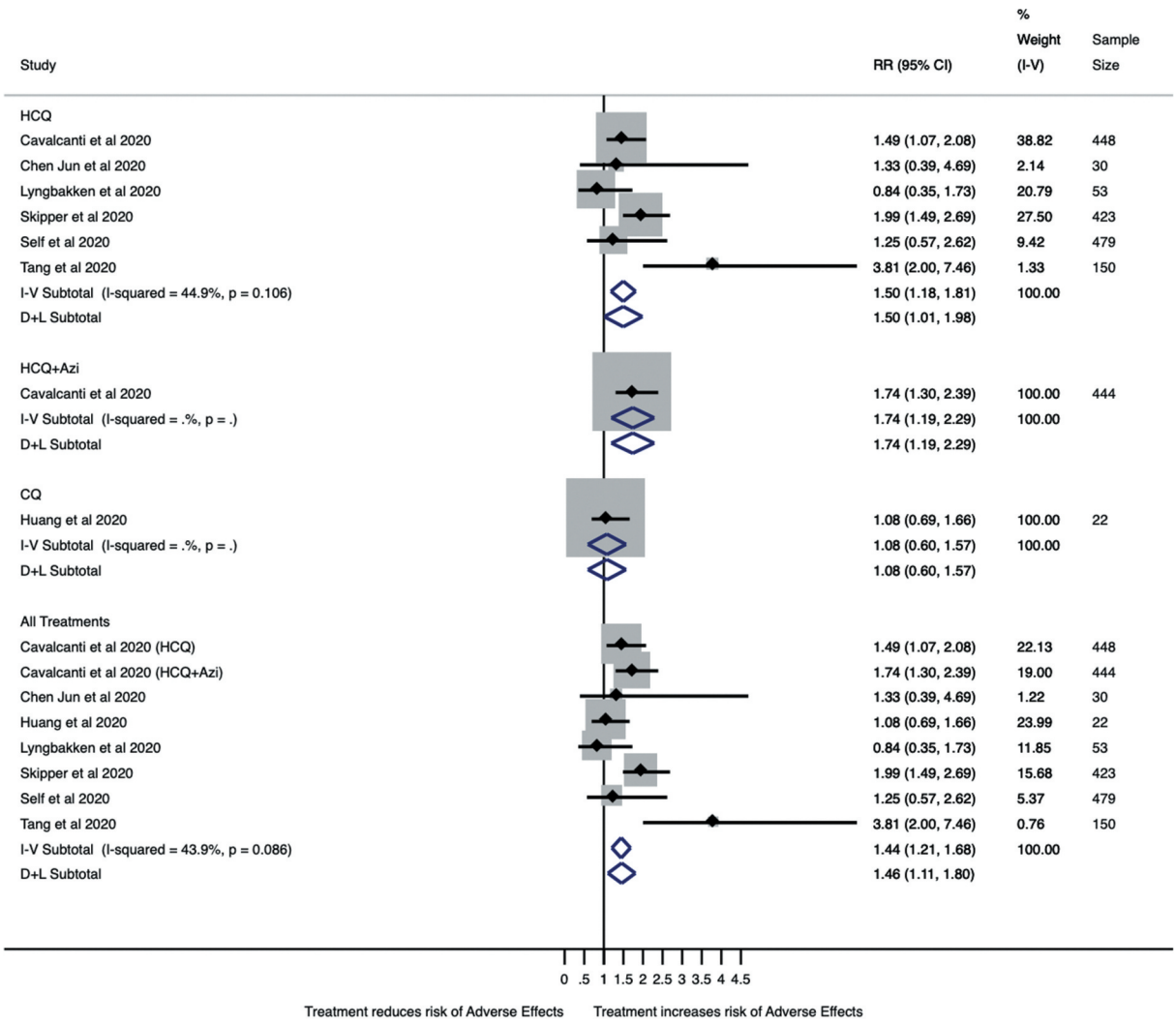

Figure 5. Effect of HCQ, HCQ+Azithromycin, and CQ use on any adverse effects risk. HCQ = hydroxychloroquine; HCQ, hydroxychloroquine plus azithromycin; CQ, chloroquine.

when compared to the control group. The results showed no statistical significance in the treatment with HCQ or CQ in achieving virological cure and faster clinical recovery.

Yao et al. [23] compared the in vitro effect of HCQ and CQ and showed that both have good antiviral activity, decreasing the replication of SARS-CoV-2. The conclusion of the study that HCQ is more potent in inhibiting viral replication led to prophylactic use. In contrast, Boulware et al. [12] show in their randomized, double-blind clinical trial that prophylactic use of HCQ after exposure to SARS-CoV-2 did not prevent patients' contamination.

The literature shows previous *in vitro* studies with Zika viruses, which demonstrated the efficacy of the antibiotic's inhibitory viral replication effect. However, the drug has not been proven to be effective in humans [24,25]. Likewise, another *in vitro* study addressing HCQ and azithromycin in the Ebola viral replication does not bring clear evidence of possible antiviral effect *in vivo* of the drugs, neither to the increase in the prevention or delay of time of death [26]. That previous evidence of *in vitro* antiviral effects made the rationale for justifying the use of those drugs as off-label therapy in the COVID-19 pandemic and was disseminated by social media in Brazil [27].

After *in vitro* studies demonstrated the efficacy of CQ and HCQ against SARS-COV-2, clinical studies were performed. Gautret et al. [8] pointed out a significant decrease in the viral load of patients infected with SARS-CoV-2 after treatment with HCQ plus azithromycin compared to the control group. Chen et al. [7] reported a faster clinical recovery in patients with COVID-19 who used HCQ. However, both clinical trials have come under strong criticism. Chen et al. [7] did not disclose the results regarding the use of different doses of HCQ, as previously specified in the study protocol, while the non-randomized clinical trial by Gautret et al. [8] was harshly questioned for the methodologies adopted and by the exclusion of six patients who had been treated with HCQ from the final results. In addition, Tang et al. [14] found no significant reduction in viral load and faster clinical recovery.

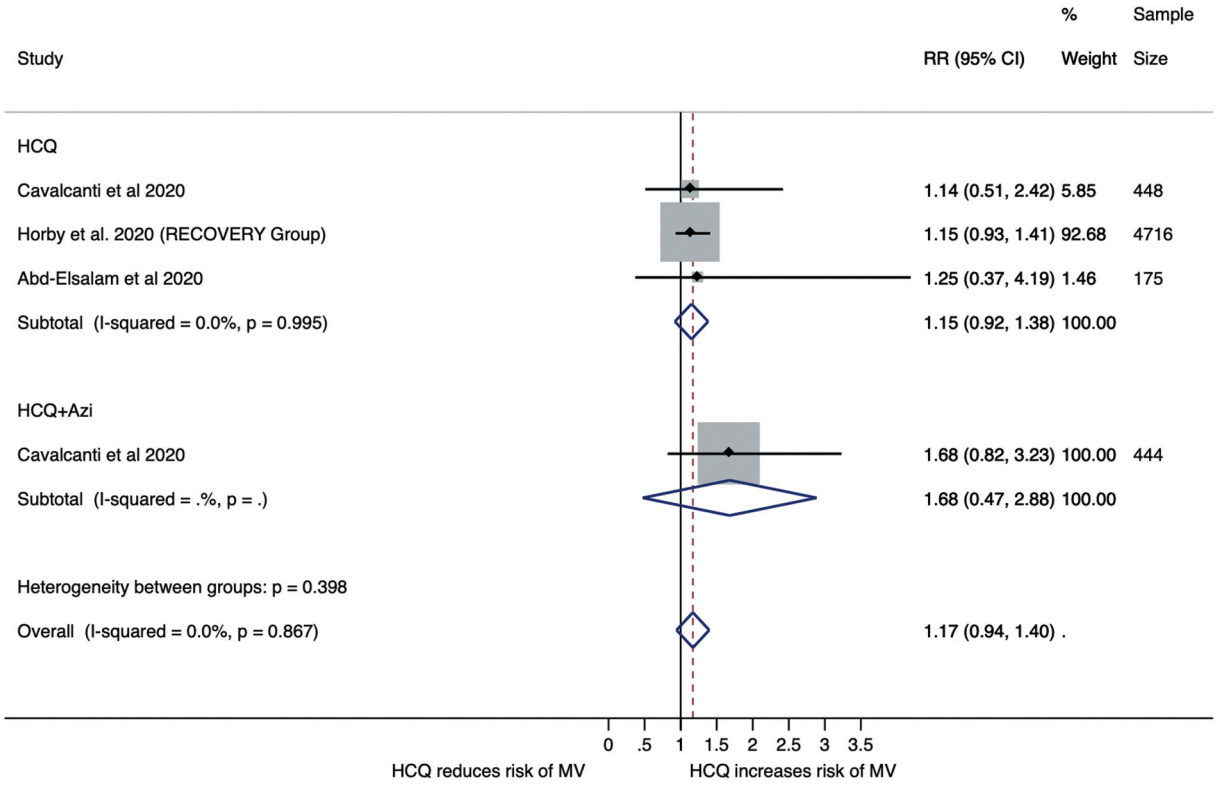

Figure 6. Effect of HCQ and HCQ+Azithromycin use on the need to use of MV. HCQ, hydroxychloroquine; HCQ, hydroxychloroquine plus azithromycin; MV, mechanical ventilation.

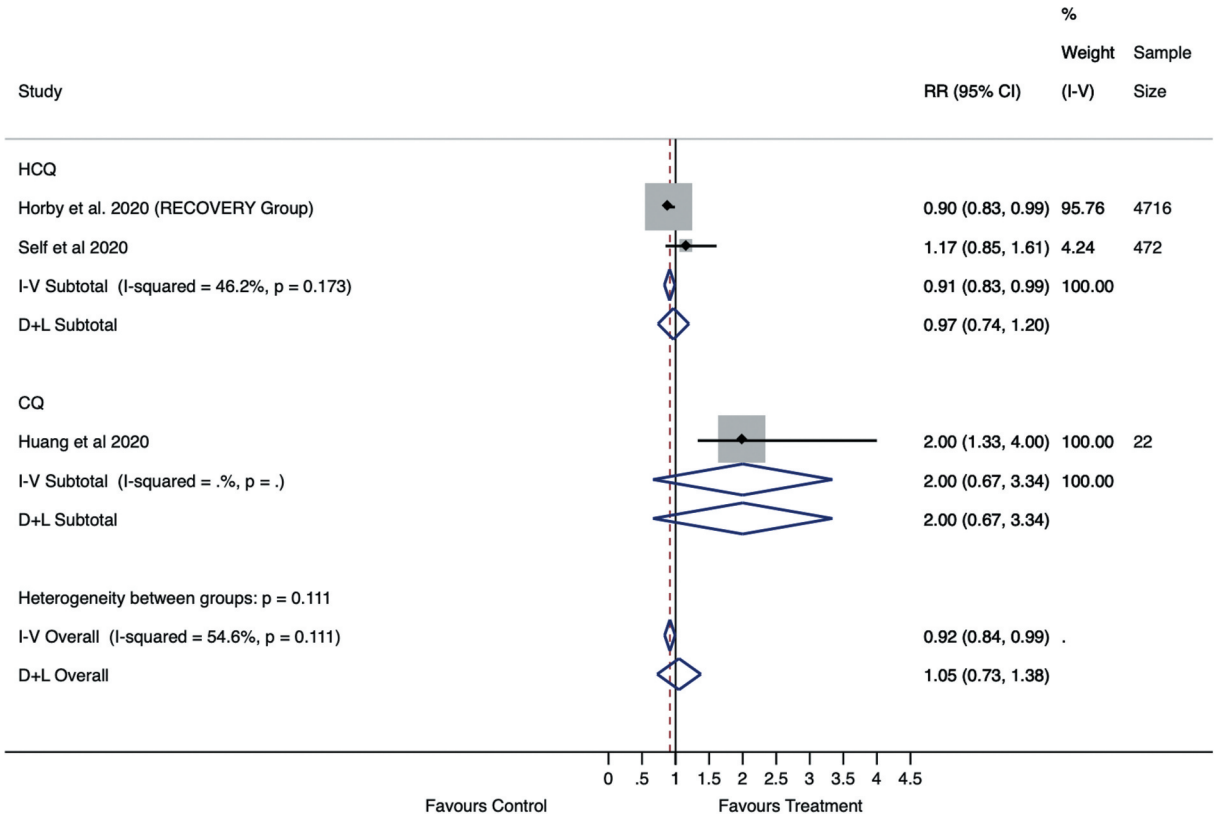

Figure 7. Effect of HCQ and CQ use on discharge from hospital. HCQ, hydroxychloroquine; CQ, chloroquine.

This review shows no association between the use of HCQ only or HCQ plus azithromycin and the improved survival of COVID-19 patients. These findings corroborate the meta-analysis of observational studies

Table 2. Sensitive analysis of the results of any adverse effects and clinical recovery.

Outcome		Any adverse effects		
Study omitted	RR	95% CI	I^2	*P*-value*
Cavalcanti et al 2020 (HCQ alone)	1.45	1.02–1.89	51.8%	<0.001
Cavalcanti et al 2020 (HCQ+Azi)	1.37	1.11–1.63	45.9%	<0.001
Chen Jun et al 2020	1.46	1.09–1.83	51.9%	<0.001
Huang et al 2020	1.55	1.29–1.83	37.8%	<0.001
Lyngbakken et al 2020	1.55	1.21–1.89	34.5%	<0.001
Self et al 2020	1.48	1.09–1.87	51.4%	<0.001
Skipper et al 2020	1.34	1.01–1.69	31.1%	<0.001
Tang et al 2020	1.48	1.10–1.74	37.9%	<0.001
Outcome		Clinical recovery		
Abd-Elsalam et al 2020	1.01	0.90–1.11	0.0%	>0.05
Cheng et al 2020	1.03	0.93–1.14	44.6%	>0.05
Huang et al 2020	1.02	0.92–1.13	47.0%	>0.05
Self et al 2020	1.03	0.93–1.14	44.6%	>0.05
Tang et al 2020	1.01	0.94–1.09	46.8%	>0.05
Zhaowei Chen et al 2020	1.00	0.93–1.08	21.4%	>0.05

* value for heterogeneity among studies assessed with Cochran's Q test.

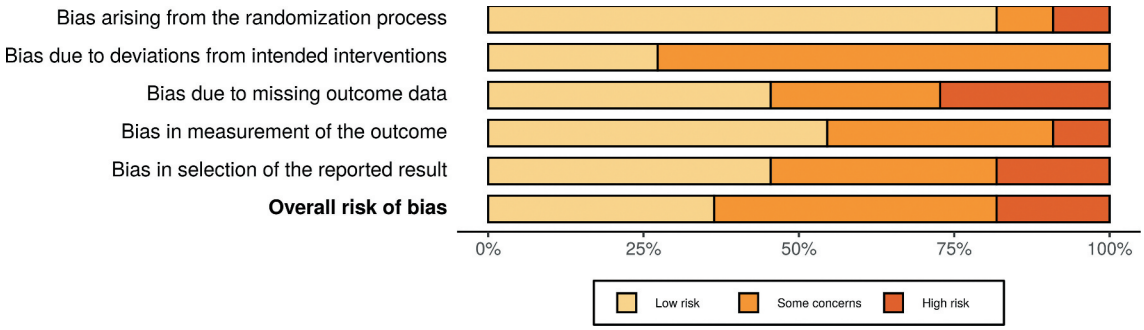

Figure 8. Quality assessment of the included studies in meta-analysis.

by Fiolet et al. [28]. The author also reports no substantial evidence to support increased mortality associated with HCQ or HCQ plus azithromycin intake.

Nevertheless, the use of these drugs in patients with COVID-19 deserves attention. Additional findings from this review show that the use of these drugs is associated with a 1.44-fold increased risk of adverse effects. The use of CQ and HCQ off-label is highly critical when addressing the adverse effects caused by these drugs. Among them, the most considered is the prolongation of the QTc interval, particularly in individuals with previous risk factors, in whom lethal ventricular arrhythmias are described, such as *Torsades de Pointes* [29].

Other effects have been described, such as psychosis, delirium, agitation, personality disorder, depression, and sleep disorders [30,31]. As for the effects of cardiac conduction, other than those already mentioned, we must consider branch block and atrioventricular block [29]. CQ and HCQ uses, when associated with azithromycin, increase the risk of hepatotoxicity [32], cardiotoxicity, and hypoglycemia [33].

Among the randomized clinical studies included in the meta-analysis, we observed a similarity between the reported adverse effects. Cavalcanti et al. [19] show that side effects were more evident in those patients who used HCQ + azithromycin, with 9 patients presenting complications due to adverse effects. Extending the QTc interval has been described in patients using HCQ and HCQ + azithromycin. Other conduction changes described were arrhythmias, bradycardia, and supraventricular tachycardia. Cavalcanti et al. [19] also highlighted the occurrence of pulmonary thromboembolism and acute kidney infection as potential complications. Vomiting, abdominal pain, changes in liver enzymes, nausea, diarrhea, skin rash, itching, coughing, and shortness of breath were other adverse effects also described [13,16,34].

Lastly, our results also suggest no association between the use of these drugs in patients with COVID-19 and the decreased need for MV and hospital discharges. Similarly, Geleris et al. [35] indicated that the risk of intubation or death was not significantly higher or lower among patients who received HCQ when compared with the control group. Furthermore, Magagnoli et al. [36] showed that the length of stay among hospitalized COVID-19 patients was not shortened by the administration of HCQ with or without azithromycin.

This study has several strengths. To our knowledge, this is the first meta-analysis using only randomized clinical trials of patients with COVID-19. This study informs physicians and patients regarding the efficiency of HCQ and CQ in treating

COVID-19. Despite the few published clinical trials, the studies selected in this systematic review a total of 7,629 patients.

Some limitations of our study were the small number of randomized trials on the use of CQ, different follow-up times between studies, studies performed without blinding, an analysis that mixed different treatments and doses and different treatments in the control group.

Conclusion

These results suggest that the use of HCQ or CQ is not associated with decreased viral load, faster clinical recovery, improved survival, decreased need for mechanical ventilation, and decreased hospitalization time for patients with COVID-19. However, it suggests that the use of HCQ or CQ can be associated with an increased risk of adverse effects.

Disclosure statement

The authors declare that there is no conflict of interests.

ORCID

Paulo Roberto Bignardi http://orcid.org/0000-0002-4730-0946
Alcindo Cerci Neto http://orcid.org/0000-0002-1702-7475

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] WHO. WHO | pneumonia of unknown cause – china. In: WHO [Internet]. World Health Organization; 2020 cited 2020 Aug 16. Available from: http://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/
[2] WHO. WHO | novel Coronavirus – china. In: WHO [Internet]. World Health Organization; 2020 cited 2020 Aug 16. Available from: http://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/
[3] WHO. Naming the coronavirus disease (COVID-19) and the virus that causes it. In: world Health Organization (WHO) [Internet]. 2020 cited 2020 Aug 16. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it
[4] WHO. Coronavirus disease 2019. 2020 cited 2020 May 6. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019
[5] Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res Springer Nature. 2020;30:269–271. .
[6] Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov Springer Nature. 2020. DOI:10.1038/s41421-020-0156-0.
[7] Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv. 2020. DOI:10.1101/2020.03.22.20040758.
[8] Gautret P, Lagier J, Parola P, 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;56:105949.
[9] Higgins JP, Savović J, Page MJ, et al. Chapter 8: assessing risk of bias in a randomized trial | cochrane Training. In Cochrane [Internet]. 2019 cited 2020 Jun 9. Available from: https://training.cochrane.org/handbook/current/chapter-08
[10] Higgins JP, Li T, Deeks JJ. Chapter 6: choosing effect measures and computing estimates of effect | cochrane training. In: Cochrane [Internet]. 2019 cited 2020 Jun 9. Available from: https://training.cochrane.org/handbook/current/chapter-06
[11] Zhang J. What's the relative risk?: a method of correcting the odds ratio in cohort studies of common outcomes. JAMA J Am Med Assoc. 2008;280:1690–1691.
[12] Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. N Engl J Med. 2020;383:517–525.
[13] Chen J, Liu D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ (Med Sci). 2020;49:1–10.
[14] Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ. 2020;369:1–11.
[15] Chen C-P, Lin Y-C, Chen T-C, et al. A multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate coronavirus disease 2019 (COVID-19). PLoS One. 2020;15:e0242763.
[16] Huang M, Tang T, Pang P, et al. Treating COVID-19 with Chloroquine. J Mol Cell Biol. 2020;12:322–325.
[17] Abd-Elsalam S, Esmail ES, Khalaf M, et al. Hydroxychloroquine in the treatment of COVID-19: a multicenter randomized controlled study. Am J Trop Med Hyg. 2020;103:1635–1639.
[18] Self WH, Semler MW, Leither LM, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: a randomized clinical trial. J Am Med Assoc. 2020;37232:2165–2176.
[19] Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. N Engl J Med. 2020;383:2041–2052.
[20] Horby P, Mafham M, Linsell L, et al. Effect of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med. 2020;383:2030–2040.
[21] Lyngbakken MN, Berdal JE, Eskesen A, et al. A pragmatic randomized controlled trial reports lack of efficacy of hydroxychloroquine on coronavirus disease 2019 viral kinetics. Nat Commun. 2020;11:6–11.
[22] Skipper CP, Pastick KA, Engen NW, et al.

Hydroxychloroquine in nonhospitalized adults with early COVID-19: a Randomized Trial. Ann Intern Med. 2020;173:623–631.
[23] Yao X, Ye F, Zhang M, 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. 2020;71:732–739.
[24] Bosseboeuf E, Aubry M, Nhan T, et al. Azithromycin inhibits the replication of zika virus. J Antivir Antiretrovir. 2018;10:6–11.
[25] Retallack H, Di Lullo E, Arias C, et al. Zika virus cell tropism in the developing human brain and inhibition by azithromycin. Proc Natl Acad Sci USA. 2016;113:14408–14413.
[26] Madrid PB, Panchal RG, Warren TK, et al. Evaluation of Ebola virus inhibitors for drug repurposing. ACS Infect Dis. 2016;1:317–326.
[27] Sattui SE, Liew JW, Graef ER, et al. Swinging the pendulum: lessons learned from public discourse concerning hydroxychloroquine and COVID-19. Expert Rev Clin Immunol. 2020;1–8. DOI:10.1080/1744666X.2020.1792778.
[28] Fiolet T, Guihur A, Rebeaud M, et al. Hydroxychloroquine and mortality risk of patients with COVID-19: a systematic review and meta-analysis of human comparative studies. Bull Cent Asia Minor Stud. 2020;1:217.
[29] McGhie TK, Harvey P, Su J, et al. Electrocardiogram abnormalities related to anti-malarials in systemic lupus erythematosus. Clin Exp Rheumatol. 2018;36:545–551.
[30] Concordia Pharmaceuticals Inc. Plaquenil ® Hydroxychloroquine Sulfate Tablets, USP Description. FDA; 2017.
[31] Good MI, Shader RI. Behavioral toxicity and equivocal suicide associated with chloroquine and its derivatives. Am J Psychiatry. 1977;134:798–801.
[32] Rasmussen SA. Psychopharmacology of COVID-19. Ann Oncol. 2020;19–21. DOI:10.1007/s00134-020-05991-x. Bizzarro
[33] Kelly M, O'Connor R, Townsend L, et al. Clinical outcomes and adverse events in patients hospitalised with COVID-19, treated with off- label hydroxychloroquine and azithromycin. Br J Clin Pharmacol. 2020;1–5. DOI:10.1111/bcp.14482.
[34] Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. medRxiv. 2020;2020.04.10.20060558. DOI:10.1101/2020.04.10.20060558.
[35] Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med. 2020;382:2411–2418.
[36] Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19. Med. 2020;1:114–127.e3.