Review Article

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The Role of Hydroxychloroquine in COVID-19 Treatment: A Systematic Review and Meta-Analysis

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Abstract

Objective: A systematic review and meta-analysis was carried out to examine the role of hydroxychloroquine (HCQ) in the treatment of COVID-19.

Methods: We performed a systematic search in PubMed, Scopus, Embase, Cochrane-Library, Web of Science, Google Scholar, and medRxiv pre-print databases using available MeSH terms for COVID-19 and hydroxychloroquine. Data from all studies that focused on the effectiveness of HCQ with or without the addition of azithromycin (AZM) in confirmed COVID-19 patients, which were published up to 12 September 2020, were collated for analysis using CMA v.2.2.064.

Results: Our systematic review retrieved 41 studies. Among these, 37 studies including 45,913 participants fulfilled the criteria for subsequent meta-analysis. The data showed no significant difference in treatment efficacy between the HCQ and control groups (RR: 1.02, 95% CI, 0.81–1.27). Combination of HCQ with AZM also did not lead to improved treatment outcomes (RR: 1.26, 95% CI, 0.91–1.74). Furthermore, the mortality difference was not significant, neither in HCQ treatment group (RR: 0.86, 95% CI, 0.71–1.03) nor in HCQ plus AZM treatment group (RR: 1.28, 95% CI, 0.76–2.14) in comparison to controls. Meta-regression analysis showed that age was the factor that significantly affected mortality (P<0.00001).

Conclusion: The meta-analysis found that there was no clinical benefit of using either HCQ by itself or in combination with AZM for the treatment of COVID-19 patients. Hence, it may be prudent for clinicians and researchers to focus on other therapeutic options that may show greater promise in this disease.

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Keywords: Azithromycin, coronavirus outbreaks, pandemic, SARS-CoV-2 disease

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Introduction

The World Health Organization (WHO) declared COVID-19 as a pandemic disease on 26 March 2020.[1,2] By 12 September 2020, the WHO COVID-19 dashboard reported that 28,329,790 people had been afflicted by COVID-19 worldwide, with a total of 911,877 deaths. There are still no officially approved therapeutic measures against COVID-19 and to date, WHO's fundamental advice to the public for prevention of this disease is the promotion of good personal hygiene, observance of social distancing, and quarantine of infectious cases.[3]

In the case of therapeutics, there are several candidate drug and non-drug treatment types classified by WHO.[4] Also, according to the Coronavirus Treatment Acceleration Program (CTAP) of the US Food and Drug Administration (FDA), as of 31 August 2020, there were approximately 590 drug development programmes, 310 trials and 5 authorised treatments only for emergency use. However, there is still no FDA-approved treatment specifically for COVID-19.[5]

Hydroxychloroquine (HCQ), used either alone or in combination with azithromycin (AZM), is one of numerous controversial therapies for COVID-19 patients that are being actively investigated. While some studies have shown promising results from the use of HCQ in preventing or treating COVID-19 infections,[6-8] other authors have reported that this drug produced no significant beneficial effects, and may even lead to harmful outcomes for patients.[9-11] The controversy has ignited heated debates not just within the scientific and medical fraternity, but in political circles as well.[12,13] This systematic review and meta-analysis aims to address this, and to provide a clearer understanding of the effectiveness of HCQ in the treatment of COVID-19.

Method

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was used for study design, search protocol, screening and reporting. A systematic search was performed using PubMed, Scopus, Embase, Cochrane Library, Web of Science and Google Scholar, as well as the pre-print database of medRxiv, to retrieve all published studies up to 12 September 2020. Additional data was extracted from gray literature and cited references of published papers. The search strategy included all MeSH terms and free keywords on COVID-19, SARS-CoV-2 and hydroxychloroquine (Table 1). The search did not impose any restriction on the date, geographical location or language of the published studies.

Table 1. Search strategy terms

PICO	Keywords	#*	Search Terms
Population	COVID-19	1	"COVID-19" OR "2019 novel coronavirus disease" OR "COVID19" OR "COVID-19 pandemic" OR "SARS-CoV-2 infection" OR "COVID-19 virus disease" OR "2019 novel coronavirus infection" OR "2019-nCoV infection" OR "2019-nCoV" OR "coronavirus disease 2019" OR "coronavirus disease-19" OR "2019-nCoV disease" OR "COVID-19 virus infection" OR "severe acute respiratory syndrome coronavirus 2" OR "Wuhan coronavirus" OR "SARS-CoV-2" OR "2019 novel coronavirus" OR "COVID-19 virus" OR "coronavirus disease 2019 virus" OR "COVID19 virus" OR "Wuhan seafood market pneumonia virus"
Intervention	Hydroxychloroquine, Azithromycin	2	"Hydroxychloroquine" OR "Oxychlorochin" OR "Oxychloroquine" OR "Hydroxychlorochin" OR "Plaquenil" OR "Hydroxychloroquine Sulfate" OR "Hydroxychloroquine Sulfate (1:1) Salt"
Comparison	–	–	–
Outcome	Clinical effectiveness, mortality, disease exacerbation, adverse effects, intubation, prophylactic effects	–	–

* #1 and #2 combined with "AND" operator

✓ To widen search results and avoid missing data, terms for azithromycin, comparison and outcomes were not included in the search strategy.

Criteria for study selection

Two researchers in the team performed screening and selection of the papers independently. A third party of the team served as the arbitrator for all disagreements. Studies that met the following criteria were included in the meta-analysis: (1) comparative or non-comparative clinical studies, including observational/interventional studies of a retrospective/prospective nature with/without control group as well as Randomised Clinical Trials (RCTs); or (2) studies that reported the effect of HCQ with/without AZM in confirmed cases of COVID-19. Papers were excluded if they were: (1) reports on in vitro or animal studies; (2) reviews; (3) case reports; (4) duplicate publications; or (5) lacking sufficient information for calculation of desired parameters.

Data extraction & quality assessment

Two researchers in the team performed quality assessment of the studies and extracted data from the selected papers independently. A third team member resolved any disagreements in this step. The data extraction checklist included the name of the first author, publication year, region of study, number of patients, number of controls, mean age, treatment option, medication dosage, treatment duration, adverse effects and nasopharyngeal culture status through Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and mortality.

The Jadad scale, ROBINS-*I* tool and Newcastle-Ottawa Scale (NOS) checklists were used to evaluate the selected randomised controlled trials, non-randomised controlled trials and observational studies, respectively, based on multiple aspects of the study methodology and study process. Risk-of-bias plots were created using the robvis online tool.[14]

Targeted outcomes

Targeted outcomes included: (1) clinical effectiveness of HCQ with/without AZM in the treatment of COVID-19; (2) mortality rates; (3) disease exacerbation; (4) frequency of known HCQ adverse effects occurring during treatment; (5) need for intubation; and (6) prophylactic effects of HCQ.

The following were performed: (1) HCQ compared to a control group that was given standard treatment; and (2) HCQ plus AZM compared to a control group that was given standard treatment.

These definitions were used to assess the outcomes:

Clinical effectiveness: nasopharyngeal swab with a negative result by RT-PCR test.

Disease exacerbation: clinical symptoms of the disease were worsened.

Adverse effects: occurrence of symptoms known to be related to HCQ, such as diarrhoea, vomiting, blurred vision, rash, headache, etc.

Group A in forest plots: case groups that received HCQ with/without the AZM regimen.

Group B in forest plots: control groups without HCQ/HCQ plus AZM regimen.

Heterogeneity assessment

I-square (I^2) statistic was used for heterogeneity evaluation. Following the Cochrane Handbook for Systematic Reviews of Interventions,[15] the I^2 was interpreted as follows: "0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity. The importance of the observed value of I^2 depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity (e.g. *P*-value from the chi-square test, or a confidence interval for I^2)."

In cases where heterogeneity was present, the DerSimonian and Laird random-effects model was applied to pool the outcomes; otherwise, the inverse variance fixed-effect model was used. Forest plots were used to visualise the degree of variation among studies.

Data analysis

Statistical analysis was performed using the Comprehensive Meta-Analysis (CMA) v. 2.2.064 software. Risk Ratio (RR) or Odds Ratio (OR) were used for outcome estimation, whenever appropriate, with 95% Confident Interval (CI). The fixed/random-effects models were used based on the heterogeneity status. In the case of zero frequency, a correction value of 0.1 was used. Meta-regression analysis was performed to examine the impact of patient age on HCQ regimen group mortality RR. However, due to unavailability of data, we could not apply meta-regression analysis on the other potential moderator variables such as sex, underlying disease, etc.

Publication bias and sensitivity analysis

Begg's and Egger's tests, as well as the funnel plot, were used for publication bias evaluation. A *P*-value of less than 0.05 was considered to be statistically significant. Additionally, we conducted a sensitivity analysis to examine the effect of studies that greatly influenced the results, especially by their weight, by excluding them from the meta-analysis.[16]

Results

Study selection process

The database search found 4,358 papers. After exclusion of duplicated papers and the initial screening, 236 papers were assessed for eligibility. Thirty-nine papers were used for qualitative synthesis, with meta-analysis performed on 37 of them. The PRISMA flow diagram of the study selection process is presented in Fig. 1.

Study characteristics

The HCQ arm of comparative studies was combined with observational studies for effect size meta-analysis of the 37 publications. The sample size of the studies ranged from 11 to 8,075, with a total of 45,913 cases. The characteristics of the studies that entered into the systematic review are shown in Table 2.

Quality assessment

Quality assessments of studies entered into the meta-analysis performed using the Jadad, ROBINS-*I* and NOS checklists are reported in Table 2. The risk of bias summary is shown in Fig. 2.

Publication bias

The Begg's and Egger's tests for every performed analysis gave insignificant results: HCQ regimen effectiveness (P_B = 0.60; P_E = 0.29); association between HCQ (P_B = 0.71; P_E = 0.41) and HCQ plus AZM (P_B = 0.25; P_E = 0.78) regimen and mortality rate in controlled randomised and non-randomised studies. However, a moderate publication bias was observed regarding overall mortality in all the studies (P_B = 0.54; P_E = 0.02).

Meta-Analysis Findings

Treatment outcome

Hydroxychloroquine regimen effectiveness

The meta-analysis of risk ratios for HCQ effectiveness in all the comparative randomised and non-randomised studies (Fig. 3) found no significant difference between

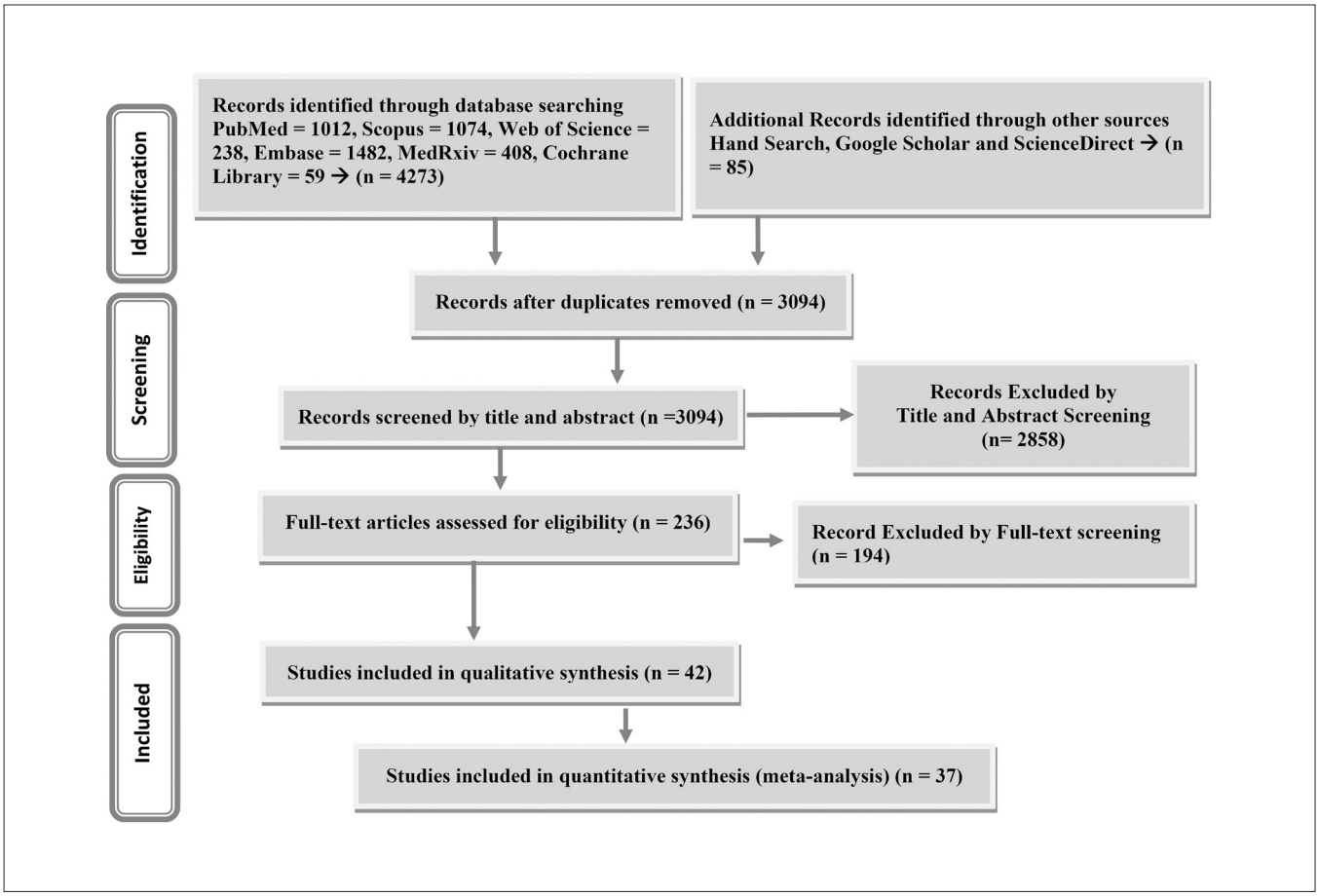

Fig. 1. PRISMA flow diagram of the study selection process

Table 2. Characteristics of studies entered into the systematic review

Study	Country	Quality Score/ Risk of Bias	Patient types	No. Patients	Cases	Controls	Treatment regimen	Duration (days)	Mean (± SD)/ Median (IQR) Age
Chen et al. 2020[17]	China	5/8*	Non-severe	62	31	31	HCQ 400 mg/d	5	44.7 (± 15.3)
Jun et al. 2020[18]	China	5/8*	-	30	15	15	HCQ 400 mg/d	5	50.5 (± 3.8)
Mahévas et al. 2020[19]	France	5/8*	Non-severe	173	84	89	HCQ 600 mg/d	-	60 (± 11.5)
Tang et al. 2020[20]	China	6/8*	Mild, Moderate, Severe	150	70	80	HCQ 400-800 mg/d	14-21	46.1 (± 14.7)
Gautret (A) et al. 2020[21]	France	8/9**	-	80	80	-	HCQ 400 mg/d + AZM	10	52.1 (± 14.8)
Gautret (B) et al. 2020[22]	France	Moderate***	-	36	14	16	HCQ 600 mg/d	6	45.1 (± 22)
			-		6	16	HCQ 600 mg/d + AZM ***(a)***		
Magagnoli et al. 2020[23]	USA	8/9**	-	368	97	158	HCQ	3-5	71 (IQR 27-99)
			-		113	158	HCQ+AZM	4-6	68 (IQR 28-95)
Molina et al. 2020[24]	France	Moderate***	Severe	11	11	-	HCQ 600 mg/d + AZM	10	58.7 (± 14.3)
Chorin et al. 2020[25]	USA- Italy	8/9**	-	251	251	-	HCQ + AZM ***(b)***	5	63 (± 15)
Barbosa J et al. 2020[26]	USA	Moderate***	-	63	32	31	HCQ 200-400 mg/d	5	62.7 (± 15)
Million et al. 2020[27]	France	6/9**	-	1061	1061	-	HCQ + AZM ***(c)***	10	43.6
Bo Yu et al. 2020[28]	China	6/9**	Critically ill	568	48	520	HCQ 400 mg/d	7-10	68 (IQR 57-76)
Membrillo et al. 2020[29]	Spain	6/9**	Mild, Moderate, Severe	166	123	43	HCQ	-	61.5(± 16,2)
Mallat et al. 2020[30]	UAE	7/9**	Mild, Moderate	34	23	11	HCQ ***(d)***	10	38.6 (± 12.5)
Lee et al. 2020[31]	South Korea	7/9**	Mild, Moderate	72	27	-	HCQ 400 mg/d	-	35 (IQR 24-55)
Carlucci et al. 2020[32]	USA	7/9**	-	521	521	-	HCQ ***(f)***	5	61.83 (± 15.97)
Rosenberge et al. 2020[33]	USA	8/9**	-	1438	735	-	HCQ + AZM	-	63
					271	-	HCQ		
Geleris et al. 2020[34]	USA	7/9**	Moderate, Severe	1376	811	565	HCQ + AZM ***(g)***	5	-
Arshad et al. 2020[35]	USA	7/8**	Severe	2541	1202	409	HCQ ***(f)***	2–5	63.7 (± 16.5)
					783		HCQ + AZM	5	
L. Chen et al. 2020[36]	China	5/8*	Mild, Moderate	30	18	12	HCQ: 200 mg BID for 10 days	10	45.67(± 14.37)
Ip et al. 2020[37]	USA	6/8**	Moderate, Severe	2512	1914	598	HCQ ***(h)***	4–5	64 (IQR 52-76)
Paccoud et al. 2020[38]	France	5/8**	Mild, Moderate, Severe	84	38	46	HCQ: 200mg TID	10	67 (± 13.5)
RECOVERY 2020[39]	UK	6/8*	-	4716	1561	3155	HCQ ***(i)***	3–10	65.3 (± 15.3)
Sbidian et al. 2020[40]	France	5/8**	Moderate, Severe	4642	623	3,792	HCQ ***(j)***	5–10	66.1 (± 18)
					227		HCQ + AZM ***(j)***		
Cavalcanti et al. 2020[10]	Brazil	6/8*	Mild, Moderate	665	221	227	HCQ: 400 mg BID	7	50.3 (± 14.6)
					217		HCQ + AZM (500 mg QD)		
Castelnuovo et al. 2020[41]	Italy	7/9**	Mild, Moderate, Severe	3451	2634	817	HCQ ***(k)***	5–10	66 (IQR 55–77)

Table 2. Characteristics of studies entered into the systematic review (Cont'd)

Study	Country	Quality Score/ Risk of Bias	Patient types	No. Patients	Cases	Controls	Treatment regimen	Duration (days)	Mean (± SD)/ Median (IQR) Age
Albani et al. 2020[42]	Italy	6/9**	–	1403	798	605	HCQ+AZM *(l)*	5–7	70 (IQR 62–75)
Lagier et al. 2020[43]	France	6/9**	–	3737	3337	162	HCQ + AZM	5–10	45 (± 17.0)
Catteau et al. 2020[44]	Belgium	6/9**	–	8075	4542	3533	HCQ *(m)*	5	71 (IQR 57-82)
Karolyi et al. 2020[45]	Austria	6/9**	–	156	20	89	HCQ *(n)*	5–10	72 (IQR 55.25–81)
Abd-Elsalam et al. 2020[46]	Egypt	6/8*	–	194	97	97	HCQ *(o)*	15	40.72 (± 19.32)
Peters et al. 2020[47]	Netherlands	7/9**	–	1893	1552	341	HCQ *(p)*	2–5	66.8 (± 14.7)
Singh et al. 2020[48]	USA	8/9**	–	1820	910	910	HCQ	–	61.45 (± 16.60)
Mitjà et al. 2020[49]	Spain	6/8*	Mild	293	136	157	HCQ *(q)*	7	41.6 (± 12.6)
Regina et al. 2020[50]	Switzerland	6/9**	–	200	83	-	HCQ	–	62.8 (± 16.17)
Okour et al.[51]	USA	6/9**	–	36	6	16	HCQ + AZM	–	–
					14		HCQ		
Saleh et al. 2020[52]	USA	7/9**	–	201	201	-	HCQ + AZM *(b)*	4–5	58.5 (± 9.1)
Barbosa Esper et al. 2020[53]	Brazil	Moderate***	–	636	412	224	HCQ + AZM *(e)*	6	62.5 (± 15.5)
Ramireddy et al. 2020[54]	USA	–	–	98	10	-	HCQ	–	62.3 (± 17)
					61		HCQ + AZM		
Studies on prophylactic effects of HCQ									
Bhattacharya et al. 2020[55]	India	8/9**	–	106	54	52	Pre-exposure HCQ	–	26.46 (± 3.93)
Boulware et al. 2020[56]	Canada	6/8*	–	821	414	407	Post-exposure HCQ *(r)*	–	40 (IQR 33-50)
Mitjà (B) et al. 2020[57]	Spain	6/8*	–	2314	1116	1198	Post-exposure HCQ *(s)*	7	48.6 (± 19.0)

IQR: interquartile range, QD: once a day, BID: twice a day, TID: three times a day
HCQ: hydroxychloroquine, AZM: azithromycin,
USA: United States of America, UAE: United Arab Emirates, UK: United Kingdom
*Quality assessed using Jadad Checklist
** Quality assessed using the Newcastle-Ottawa Scale Checklist.
*** Risk of Bias assessed using ROBINS I tool.
(*a*) 500 mg on day1 followed by 250mg per day, the next four days.
(*b*) Hydroxychloroquine 400 mg by mouth twice daily for one day followed by 200 mg by mouth twice daily for four days, and azithromycin 500 mg by mouth or intravenous daily for five days.
(c) HCQ (200 mg three times daily for ten days) + AZM (500 mg on day 1 followed by 250 mg daily for the next four days).
(d) HCQ 400 mg was administered twice daily for 1 day, followed by 400 mg daily for 10 days.
(e) Hydroxychloroquine 800mg on the first day and 400mg for another 6 days and azithromycin 500 mg once daily for five days.
(f) 400 mg load followed by 200 mg twice daily for five days.
(g) The suggested HCQ regimen was a loading dose of 600 mg twice on day 1, followed by 400 mg daily for 4 additional days. Azithromycin at a dose of 500 mg on day 1 and then 250 mg daily for 4 more days in combination with HCQ was an additional suggested therapeutic option.
(h) 800 mg on day 1, and 400 mg on day 2-5 (80%, n=1533), followed by 200 mg TID
(i) 4 tablets (800 mg) at zero and 6 hours, followed by 2 tablets (400 mg) starting at 12 hours after the initial dose and then every 12 hours for the next 9 days or until discharge.
(j) HCQ: Loading dose of 600 mg on day 1, followed by 400 mg daily for 9 additional days. AZM: At a dose of 500 mg on day 1 and then 250 mg daily for 4 more days.
(k) HCQ was administered at dose of 400 mg x2/day or x4/day the first day, and 200 mg x2/day from the second day onwards for at least 5 to a maximum of 10 days, according to the clinical evolution of the disease
(l) 500 mg per day for 5 days for azithromycin and 200 mg bid for 5–7 days for hydroxychloroquine, based on the judgment of the treating physician.
(m) 2400 mg in total over 5 days
(n) The HCQ was administered with a loading dose of 400 mg twice daily on the first day, followed by 200 mg twice daily
(o) HCQ 400 mg twice daily (in day 1) followed by 200 mg tablets twice daily added to the standard of care treatment
(p) hydroxychloroquine sulphate was 400 mg twice daily on the first day, followed by 200 mg twice daily on days 2 to 5
(q) 800 mg on day 1, followed by 400 mg once daily for 6 days
(r) 800 mg (4 tablets) once, then 600 mg (3 tablets) 6 to 8 hours later, then 600 mg (3 tablets) daily for 4 more days for a total course of 5 days (19 tablets total).
(s) HCQ (Dolquine®) 800 mg on day 1, followed by 400 mg once daily for six days

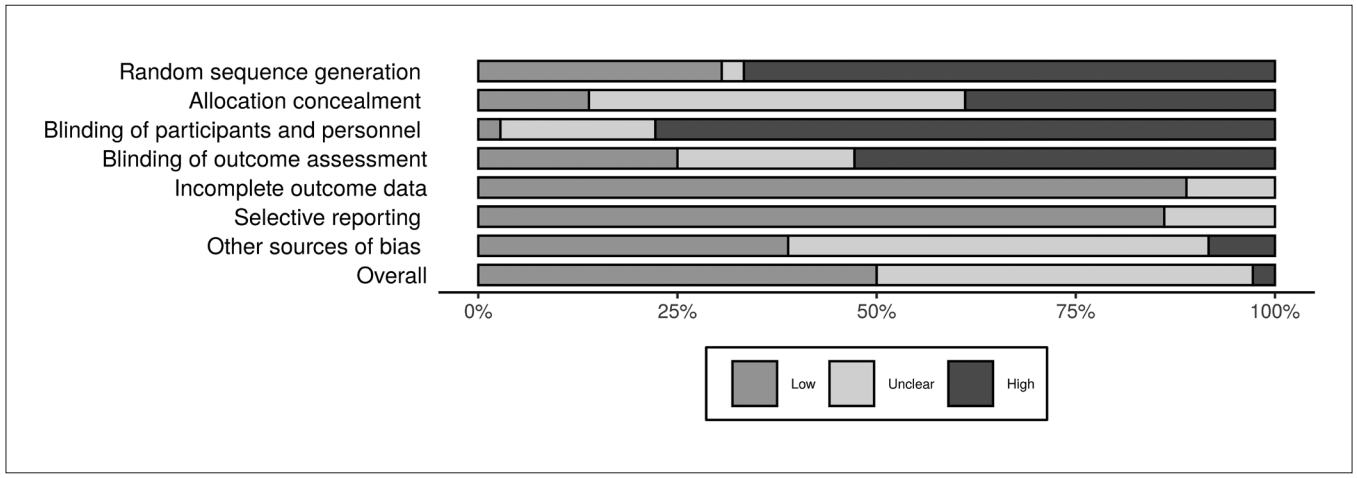

Fig. 2. Summary of risk of bias for studies entered into the meta-analysis

the case group (standard treatment with HCQ regimen) and the control group (standard treatment without HCQ; RR: 1.02, 95% CI, 0.81–1.27; RD: 0.01, 95% CI, -0.12–0.15). Meta-analysis of controlled randomised studies showed no substantial effectiveness of HCQ (RR: 1.19, 95% CI, 0.87–1.63; RD: 0.12, 95% CI, -0.07–0.33).

Sensitivity analysis for hydroxychloroquine regimen effectiveness

To evaluate the impact of inverse RRs as well as the weight of different studies on the meta-analysis results, we conducted several sensitivity analyses. (1) Despite

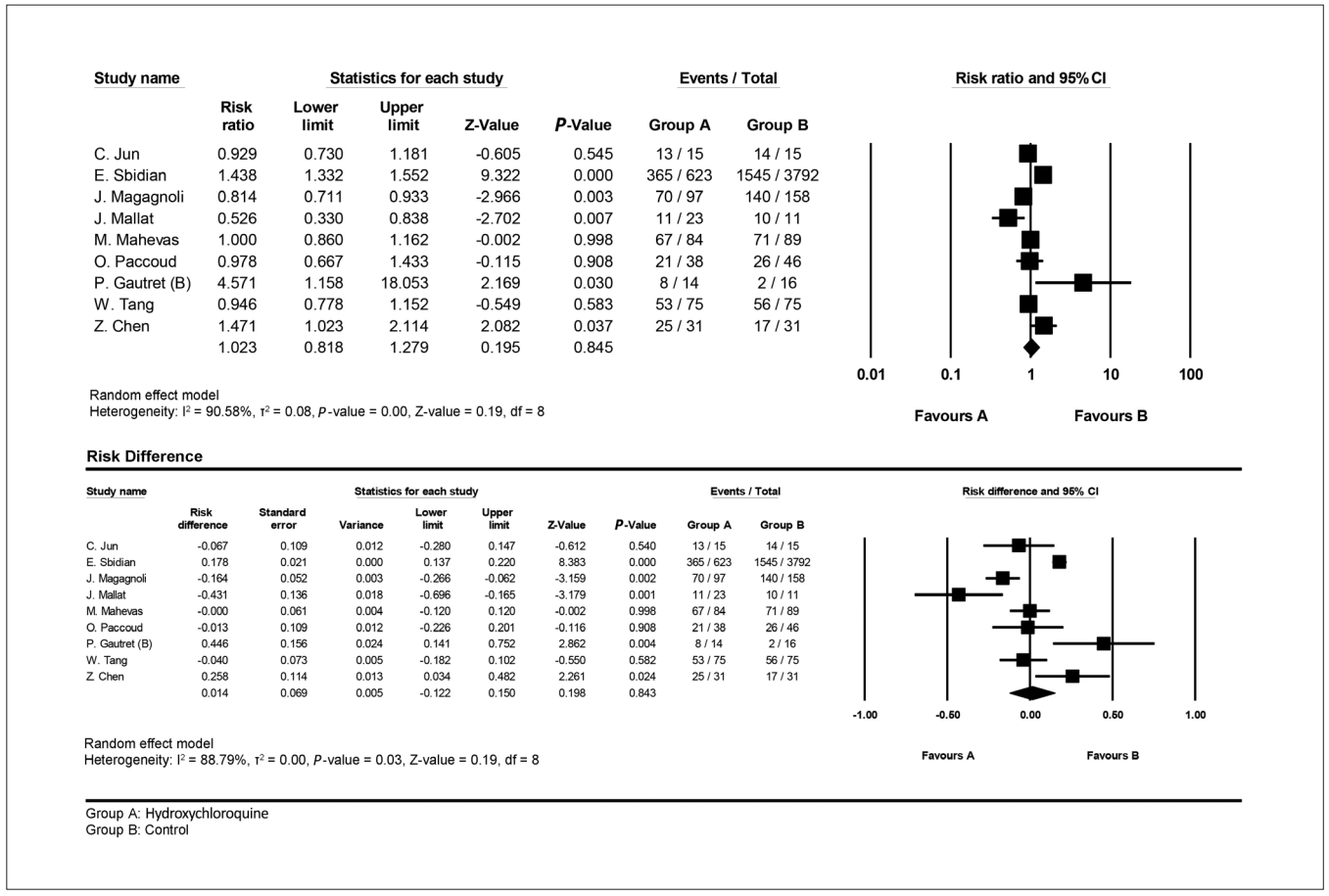

Fig. 3. Forest plot for pooling risk ratios and risk differences regarding hydroxychloroquine regimen in comparative randomised and non-randomised studies

the substantial relative weight of the Sbidian et al. study, exclusion of this study from the meta-analysis did not significantly change the results (RR: 0.94, 95% CI, 0.80–1.11). (2) Of the 5 studies that reported *P*-values of less than 0.05, 3 have a *P* value less than 0.05 in favour of Group A and 2 have a *P*-value below 0.05 in favour of Group B. These are the Magagnoli et al. and Mallat *et al.* studies, in which the 95% CI of the RR does not intersect with that from the Chen et al., Gautret (B) et al. and Sbidian et al. reports. Excluding the papers by Magagnoli et al. and Mallat et al. from the sensitivity analysis did not have any effect (RR: 1.14, 95% CI, 0.92–1.41). (3) Exclusion of these studies showed no significant difference in the meta-analysis (RR: 0.89, 95% CI, 0.78–1.00). (4) To maximise the analysis validity, exclusion of pre-prints data from meta-analysis did not significantly change the results (RR: 0.93, 95% CI, 0.82–1.06).

Hydroxychloroquine plus azithromycin regimen

No significant difference was found in the effectiveness of the HCQ plus AZM combination regimen compared to the control group in the meta-analysis (RR: 1.26, 95% CI, 0.91–1.74). A considerable risk difference was present between the groups (RD: 0.28, 95% CI, 0.01–0.54). Also, by excluding pre-prints data from meta-analysis, sensitivity analysis showed no significant differences for HCQ plus AZM regimen (RR: 2.28, 95% CI, 0.37–13.79).

Hydroxychloroquine regimen and mortality rate

Meta-analysis of comparative randomised and non-randomised studies showed no significant difference in mortality rates between the HCQ regimen group and standard treatment group (RR:0.86, 95% CI, 0.71–1.03; RD: -0.02, 95% CI, -0.04–0.00). The sensitivity analysis found no significant difference in the mortality rate in the HCQ regimen arm compared to the control group by excluding pre-prints data (RR: 0.86, 95% CI, 0.67–1.10).

Meta-regression analysis of the effect of age on mortality

Meta-regression showed that the age of patients had a significant effect on risk ratios with regard to mortality rate in the HCQ regimen group ($P<0.00001$).

Hydroxychloroquine plus azithromycin regimen and mortality rate

Meta-analysis of mortality rates in comparative randomised and non-randomised studies found no significant difference in the HCQ plus AZM regimen group compared to the control group (RR: 1.28, 95% CI, 0.76–2.14; RD: 0.09, 95% CI, -0.02–0.20). Also, the sensitivity analysis result was not significant after excluding pre-prints (RR: 1.28, 95% CI, 0.59–2.79).

Overall mortality

In the analysis of overall mortality, we considered the treatment arms of all comparative studies as observational studies. The pooled overall mortality rate was found to be 15.5% (95% CI, 13.2%–18.0%) for HCQ and 9.5% (95% CI, 5.2%–16.8%) HCQ plus AZM regimen (Fig. 4). By excluding pre-prints from meta-analysis, the results did not change substantially.

Disease exacerbation

Meta-analysis of all comparative studies showed that disease exacerbation was not significantly different between the HCQ group and the control group (RR: 1.41, 95% CI, 0.82–2.44; RD: 0.03, 95% CI, -0.03–0.11). Exclusion of pre-prints data from meta-analysis did not significantly change the results (RR: 1.50, 95% CI, 0.84–2.67). Meta-analysis of controlled randomised studies found no difference in disease exacerbation between two groups (RR: 0.62, 95% CI, 0.20–1.96; RD: -0.04, 95% CI, -0.13–0.05).

Intubation

Meta-analysis of comparative randomised and non-randomised studies found no significant difference between the HCQ group and the control group in the odds of intubation during treatment (OR: 2.06, 95% CI, 0.31–13.52).

Adverse effects

Meta-analysis of comparative randomised and non-randomised studies showed that the odds of adverse effects in patients who received the HCQ regimen was approximately 3.5 times higher than the control group without HCQ regimen (OR: 3.40, 95% CI, 1.65–6.98). Meta-analysis of controlled randomised studies found 4 times higher odds of experiencing adverse effects in patients who received the HCQ regimen compared to the control group (OR: 4.08, 95% CI, 1.84–9.04). Exclusion of pre-prints from meta-analysis resulted in approximately 3 times higher chance of adverse effects (OR: 3.03, 95% CI, 1.34–6.86).

Meta-analysis of observational studies

We considered the treatment arms of comparative studies as observational studies in this section. Meta-analysis showed that 26.8% of patients suffered from known HCQ adverse effects (95% CI, 16.3%–40.7%); 65.3% (95% CI, 56.7%–73.1%) of patients were discharged

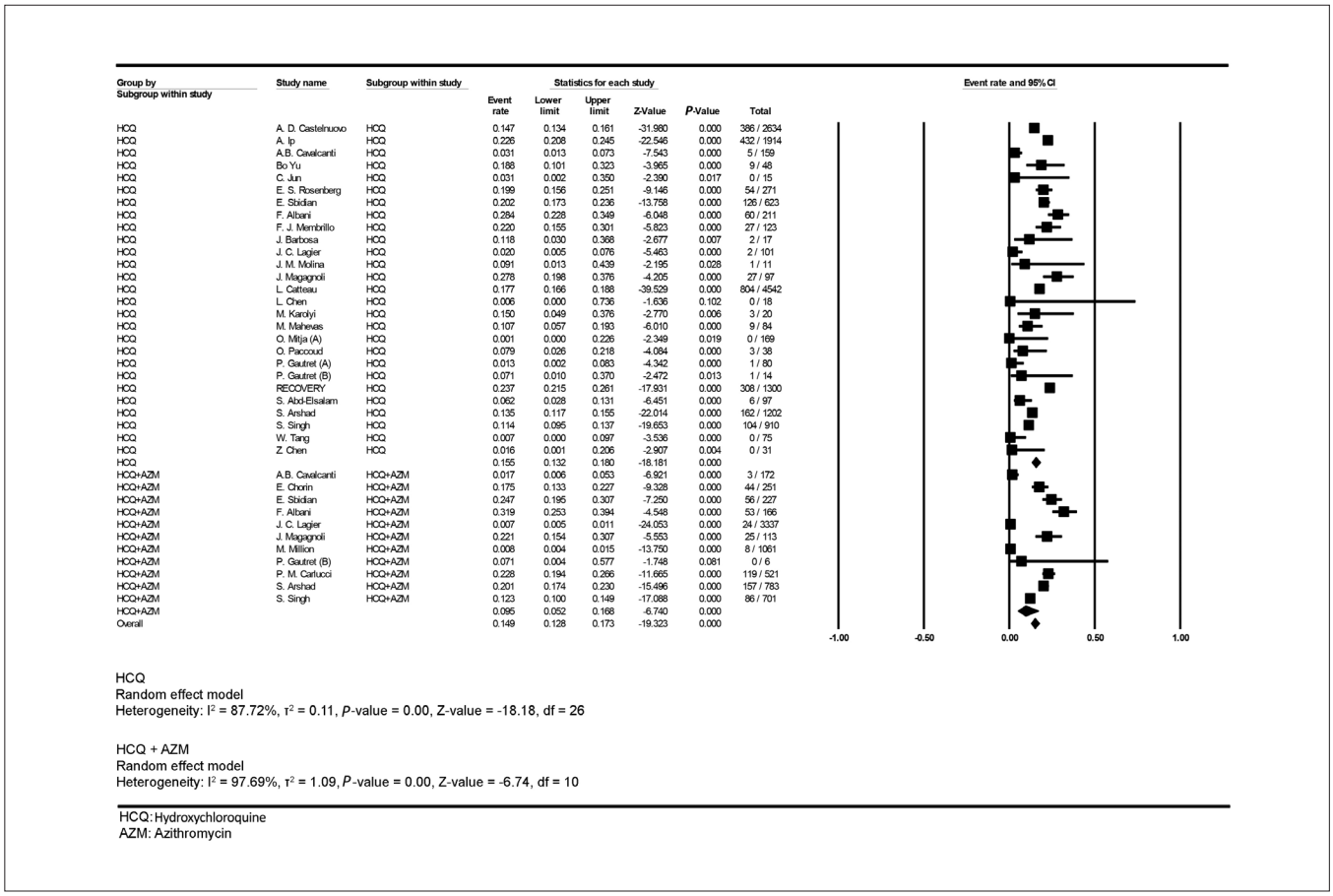

Fig. 4. Forest plot for pooling mortality rates

from hospitals or had negative RT-PCR results from their nasopharyngeal culture. In contrast, 23.3% (95% CI, 8.9%–48.6%) of patients suffered exacerbated disease, with 7.1% (95% CI, 2.8%–17.0%) being admitted to the intensive care unit (ICU) and 23.8% (95% CI, 6.6%–57.9%) undergoing intubation.

Prophylactic effects of hydroxychloroquine

Meta-analysis revealed no significant prophylactic effect of HCQ (OR: 0.58, 95% CI, 0.20–1.66).

Discussion

The natural course of COVID-19 is such that more than 90% of patients will recover spontaneously from the infection. However, in a small proportion of cases, the disease progresses and leads to the development of Acute Respiratory Distress Syndrome and multi-organ failure.[58] Recent reports suggest that this progression may be due to cytokine storm, in which there is an uncontrolled release of pro-inflammatory cytokines into the plasma of patients. Thus, there is a critical need to identify anti-inflammatory agents to reduce the production and release of cytokines and pro-inflammatory factors.[59]

From as early as the 1950s, HCQ has been known to be an effective anti-inflammatory drug that is especially useful for the treatment of autoimmune disorders.[60] A recent report by Yao et al. showed that HCQ may play an inhibitory role in SARS-CoV-2 infection in vitro.[61] Pagliano et al. suggested that HCQ may be used as a pre/post-exposure prophylaxis agent against SARS-CoV-2 infection for healthcare workers who were exposed to the virus in a contaminated environment.[62]

In contrast, Guastalegname and Vallone urged caution as the usefulness and potential harmful effects of HCQ in COVID-19 were not clear, and pointed out that treatment of Chikungunya viral infection with chloroquine led to dire paradoxical consequences.[9,63] A similar cautionary opinion was also expressed by Kim et. al.[64] Molina et al. followed up on 11 COVID-19 patients who were treated with an HCQ and azithromycin regimen, and found no clinical benefit or anti-viral activity.[24] The pre-print of a quasi-randomised comparative study showed that

HCQ not only did not provide any benefits to patients with COVID-19 but also increased the need for urgent respiratory support (P=0.013).[26] Similarly, Magagnoli et al. found that HCQ/HCQ plus AZM regimens failed to provide any clinical benefits to COVID-19 patients.[23] Instead, patients in the HCQ group had a higher mortality rate (hazard ratio: 2.61, 95% CI, 1.10–6.17; P=0.03). Similarly, the target trial emulation on 181 patients with SARS-CoV-2 hypoxic pneumonia did not support the effectiveness of the HCQ regimen.[65]

Adding to the controversy, the observational study by Geleris et. al. found no evidence of beneficial or harmful outcomes in the use of HCQ for treating patients with COVID-19.[34] A separate study by Rosenberg et al. reported that HCQ/AZM treatment was not associated with in-hospital mortality.[33] The multinational RECOVERY Collaborative Group demonstrated that HCQ administration was not associated with a reduction in 28-day mortality in 4,716 patients. However, there was an increased risk of lengthening the hospital stay, progression to invasive mechanical ventilation or death.

We aimed for this systematic review to help to clear up the controversy surrounding usage of HCQ for COVID-19 treatment. Our meta-analysis found no significant differences in effectiveness of treatment or mortality rates in patients who received either the HCQ or the HCQ plus AZM regimens versus those who were given standard therapy. Furthermore, patients who were given HCQ experienced known adverse effects of HCQ, including vomiting, diarrhoea, blurred vision, rashes, headache, etc.

Interestingly, the findings from our meta-analysis differ from those done by Sarma et al., who analysed 3 studies and concluded that HCQ may have promising effects in the management of COVID-19 patients.[13] Million et al.[12] also carried out a meta-analysis on the first available reports on COVID-19 released in *IHU Méditerranée Infection*. They found a promising trend of beneficial effects of chloroquine derivatives in the treatment of COVID-19, and suggested prescribing HCQ as a Grade I recommendation. Several possible reasons may have contributed to these different conclusions, one of which is that heterogeneity and the pattern of dispersion in the results were not considered by the other researchers. Additionally, the other authors combined treatment outcomes in unusual ways and used odds ratios only in their analysis, whereas risk ratios have higher priority and are the preferred statistic. It is also of concern that non-randomised trials were included in their meta-analyses.

Conclusion

This systematic review and meta-analysis found no clinical benefits in the use of HCQ, either alone or in combination with AZM, in the treatment of COVID-19. Instead, patients who were given HCQ experienced adverse effects more frequently. It is worth noting that, based on the recommendation of the international steering committee, WHO has discontinued the HCQ and lopinavir/ritonavir treatment arm for the Solidarity Trial on 4 July 2020.[66] It remains unclear whether hydroxychloroquine is effective for COVID-19 prophylaxis.

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