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Review Article - Covid-19 Series

Effect of Chloroquine and Hydroxychloroquine on COVID-19 Virological Outcomes: An Updated Meta-Analysis

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Abstract

As anti-malarial drugs have been found to inhibit Corona viruses in vitro, studies have evaluated the effect of these drugs inCOVID-19 infection. We conducted an updated meta-analysis of clinical trials and observational studies published till June 2020. Patients with reverse transcription polymerase chain reaction (RT-PCR) confirmed Severe Acute Respiratory Syndrome Coronavirus 2 (COVID-19) infection were included. The drugs used in the intervention group are Chloroquine (CQ)/Hydroxychloroquine (HCQ) with or without Azithromycin. The primary outcome is time to achieve virological cure. Of 1040 citations, 11 studies provided data of 1215 patients. Compared to control, CQ/HCQ has no significant effect on the time to negative COVID-19 RT-PCR results, neither in clinical trials (mean difference [MD] 1.55; 95% confidence interval [CI] - 0.7 to 3.79; P = 0.18; n = 180), nor in observational studies (MD 1.14; 95%CI - 11.98 to 14.26; P = 0.86, n = 407). CQ/HCQ did not affect the virological cure after day 3, 7, 10, 14, 21 and 28; except after day 5, as shown by a single small non-randomised trial (odds ratio [OR] 9.33; 95% CI 1.51 to 57.65; P = 0.02, n = 30). Pooled data from 2 observational studies showed a significant effect of CQ/HCQ on virological cure by after day 10 (OR 7.86; 95% CI 4.4 to 14.04, P < 0.001, n = 373) and day 14 (OR 6.37; 95% CI 3.01 to 13.48, P < 0.001, n = 407). The GRADE evidence generated was of "very low-quality/certainty". To conclude, CQ/HCQ does not affect the time to virological cure compared to usual/standard of care in COVID-19 infection. Recurrent infection in a smaller number of patients was noted in the CQ/HCQ group. As the evidence generated was of "very low-quality/certainty)", large good quality studies are needed to confirm the present findings.

Keywords: Aminoquinoline, azithromycin, COVID-19, evidence-based medicine, hydroxychloroquine, severe acute respiratory syndrome coronavirus 2

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19, a highly contagious disease emerged in Wuhan, China, in late 2019.[1] Till date, it has infected millions of patients globally. India has a rising number of cases but the mortality is low.[2] As there is no specific anti-viral drugs, pharmaceutical agents (antiviral agents, antibiotics, immune-modulators and convalescent plasma) are being tried with variable success.[3]

Two aminoquinoline anti-malarial drugs (chloroquine [CQ] and hydroxychloroquine [HCQ]) were in the news for treatment of COVID-19 infection, after publication of one study from France.[4] Subsequently, large studies (mainly observational) have been published.[5] Both the drugs have been found to inhibit other corona viruses, such as SARS-CoV-1.[6,7] The mechanisms of action include – inhibition of angiotensin converting enzyme 2 (ACE-2) used by the virus for entry into the cell,[8,9] inhibition of release of viral particles into intra-cellular space,[10,11] and a non-specific anti-inflammatory action (inhibition of interleukin-6 [IL-6], tumour necrosis factor, aberrant interferon and other pro-inflammatory cytokines that cause lung injury leading to acute respiratory distress syndrome).[10,12] Both the drugs are cheap, and considered safe, as per their approved indications. Compared to CQ, HCQ is more soluble and less toxic and is considered safer.[13,14]

There have been published studies evaluating the safety and/or efficacy of these agents (alone or in combination)

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compared to a control arm or parallel intervention, to treat patients with COVID-19.[4,15-24] However, the results have been contradictory. A published rapid systematic review including data from three studies found no role of anti-malarial drugs on the virological outcomes in patients with COVID-19 infection.[25] After publication of this review, many studies (both observational studies and clinical trials) with larger sample sizes have been published. The present updated meta-analysis has included these larger studies to evaluate the effect of the anti-malarial drugs (CQ and HCQ) to inform clinical practice, and guide the international agencies to formulate recommendation.

Materials and Methods

Types of studies

Both clinical trials and observational studies comparing anti-malarial drugs (CQ and HCQ) alone or in combination with other drugs *versus* control (standard of care) or other treatment were included.

Types of participants

Children (age >12 years) and adults with reverse transcription-polymerase chain reaction (RT-PCR) confirmed SARS CoV-2 (COVID-19) cases treated in the hospital were included. Exclusion criteria were allergy to these anti-malarial drugs, hearing loss, retinopathy and severe neuro-psychiatric diseases.

Types of interventions

Anti-malarial drugs (CQ and HCQ) administered (with or without Azithormycin) in various dose schedules to patients with SARS-CoV-2 (COVID-19) infection.[13] Control group patients received usual/standard of care as per the hospital/institute policy or government guideline. Studies comparing different doses (high-dose versus low-dose of anti-malarial drugs) were also included.

Types of outcome measures

Primary

1. Time to virological cure (days).

Secondary

1. Proportion of patients with virological cure after days 3, 5, 7, 10, 14, 21 and 28
2. Proportion of patients with recurrence of infection.

Definition of outcome measures: Virological cure is defined as non-detection (negative report) of COVID-19 by RT-PCR in two consecutive respiratory specimens (naso-pharyngeal swabs, throat swabs, nasal swab, broncho-alveolar lavage fluid and tracheal aspirate) taken 24 h apart. Recurrence of infection is defined as detection (positive report) of COVID-19 by RT-PCR in any of the above specimens collected from a patient at any time point after documentation of virological cure.[26]

Search methodology

Major databases (PubMed/MEDLINE, Cochrane Central Register of Controlled Trials [CENTRAL], EMBASE, Google Scholar and Pre-print servers [medRxiv, bioRxiv, OSF preprints, preprints.org]) were searched systematically from 1970 to 5th June 2020 [Appendix 1]. No language restrictions were applied. Two reviewers (SSN, BB) reviewed the search results to identify relevant studies.

Data extraction

Data extraction was done using a data extraction form that was designed and pilot tested *a priori*. Two authors (BB and BM) independently extracted the following information from each study: author year, country, study design, setting (hospital or community), method of recruitment, inclusion criteria, risk of bias, participants (age, sex, sample size, disease severity), intervention (dosage, duration, frequency, and co-intervention if any), outcomes (outcome definition, valid unit of measurement, time points of collection, and reporting), loss to follow-up and key conclusions. Any disagreements between the two review authors were resolved through discussion with the third author (RRD).

Assessment of risk of bias in the included studies

Two review authors independently (BB, SSN) assessed the methodological quality of the selected trials by using Cochrane Handbook,[27] and of observational studies by Newcastle Ottawa Scale.[28] Quality assessment was undertaken using the ROBINS-I tool for non-randomised trials.[29] Any disagreements between the two review authors were resolved through discussion with the third author (RRD).

Data synthesis

Data were analysed using Review Manager (RevMan) V.5.1.[30] Data were pooled and expressed as mean difference (MD) with 95% confidence interval (CI), if continuous; odds ratio (OR) with 95% CI, if categorical. All the analyses were by Generic Inverse Variance method using random effects weighting,[31] where the log RRs for cohort studies or log ORs for case–control studies were weighted by the inverse of the variance to obtain a pooled RR estimate. A $P < 0.05$ was considered statistically significant. Inter-study heterogeneity was assessed by Cochrane's Q (Chi-square $P < 0.10$) and quantified by I^2. An I^2 ≥50% indicated 'substantial' heterogeneity and ≥75% indicated 'considerable' heterogeneity.[32]

Grade of evidence

To assess the quality of evidence, we used GRADE Profiler software (V.3.2) (Hamilton, Canada).[33,34] The software uses five parameters for rating the quality of evidence (risk of bias, inconsistency of results, indirectness of evidence, imprecision of results and publication bias), and does rating as-no, serious and very serious limitation.

Results

Description of studies

Of 1040 total citations retrieved, the full text of 15 papers was assessed for eligibility, and 4 studies were excluded [Figure 1]. Of the remaining 11 eligible studies (n = 1215), 6 were published in peer-reviewed journals,[4,15-19] and 5 in pre-print servers (not peer-reviewed).[20-24] We contacted the authors of

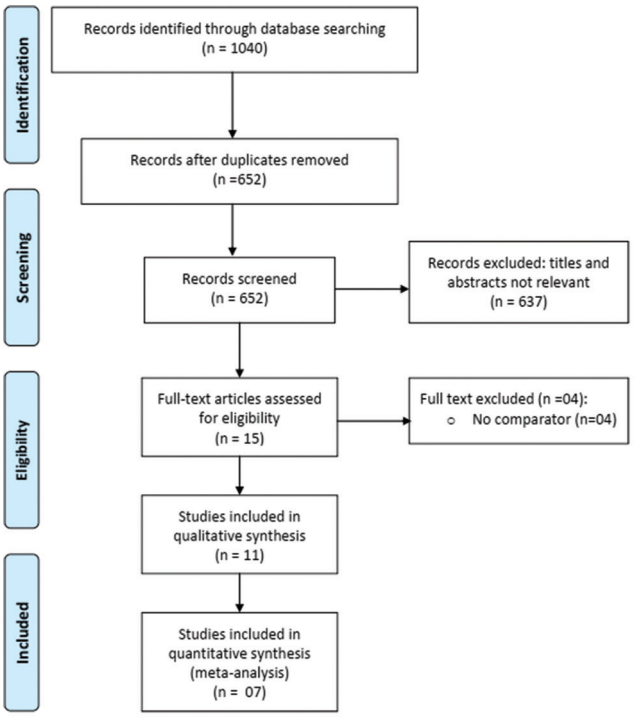

Figure 1: PRISMA flow diagram

these 5 studies to provide us the permission to use their data in the meta-analysis, but only one study author responded.[20] Hence, we included the data of this study along with other published studies (in peer-reviewed journals) in the present meta-analysis [Table 1], and described the characteristics of rest 4 studies[21-24] [Table 2]. Of the 7 included studies ($n = 726$), 5 clinical trials provide data of 319 patients, and the 2 observational studies provided data of 407 patients.[4,15-20] A total of 415 patients received HCQ or CQ (clinical trials = 195, observational studies = 220), and 6 received a combination of HCQ plus Azithromycin (in one non-RCT [non-randomised controlled trials]).[4] The studies were conducted in the following countries: Chin ($n = 4$, 575 patients), Brazil ($n = 1$, 81 patients), France ($n = 1$, 36 patients) and UAE ($n = 1$, 34 patients). One trial compared high versus low-dose of Chloroquine.[18] Of the 5 clinical trials, 2 were double-blind and 1 was a non-RCT.

As shown in Table 1, the age of included participants, severity of illness, dose schedule and timing of the administration of intervention (HCQ/CQ) varied widely among the studies. Contrary to CQ, the dose schedule of HCQ varied widely. No study was able to start the intervention (HCQ/CQ) in the early phase of illness (within 48 h of symptom onset), which is regarded as the golden window for antiviral treatment (e.g. in influenza).[35]

Risk of bias in included studies

The details have been provided in Supplemental file [Appendix 2]. Except one trial,[18] others had low to high-risk of bias in different domains. One non-RCT had serious risk of biases in all the domains.[4] All the observational studies were at a high risk of bias for selection of controls, and a low risk of bias for the exposure parameters.

Effect of interventions

Primary outcomes

1. Time to virological cure (days): The pooled result from 2 RCTs showed no significant difference between the HCQ group and control group [MD 1.55 (95% CI - 0.7 to 3.79), $P = 0.18$) [Figure 2]. The pooled result from two observational studies also showed no significant difference between the HCQ group and control group [MD 1.14 (95% CI - 11.98 to 14.26), $P = 0.86$) [Figure 3].

Secondary outcomes

1. Proportion of patients with virological cure after days 3, 5, 7, 10, 14, 21 and 28: Compared to control, CQ/HCQ did not affect the virological cure after days 3, 7, 21 and 28 [Table 3]. However, the pooled data from 2 observational studies showed a significant effect of CQ/HCQ on virological cure after 10 and 14 days [Table 4].
2. Proportion of patients with recurrence of infection: Two studies reported this outcome.[4,19] In one study, 1 of 20 patients (5%) in the HCQ group tested positive on day 8 (was negative on day 6).[4] In the other study, 3 of 197 patients (1.5%) in the CQ group tested positive (from faecal sample, not from naso-pharyngeal samples) within 7 days following hospital discharge.

Grade of evidence

The evidence generated was of 'very low-quality' for all the outcomes (primary and secondary). A detailed analysis of the summary of evidence is provided in Table 5.

Discussion

Summary of evidence

After an extensive search of the literature we could find 11 studies ($n = 1215$) eligible for inclusion in the review. Compared to control, CQ/HCQ has no significant effect on the time to negative COVID-19 RT-PCR results. CQ/HCQ des not affect the virological cure after days 3, 7, 10, 14, 21 and 28 (except after day 5 as shown by a single, small non-RCT). However, pooled data from 2 observational studies showed a significant effect of CQ/HCQ on virological cure after 10 and 14 days. Two studies reported repeat COVID-19 positive with all the patients belonging to the CQ/HCQ group. The GRADE evidence generated for all outcomes was of 'very low-quality'.

It has to be kept in mind that, the anti-viral action of anti-malarial drugs against COVID-19 is still largely unknown.[36] The dose schedule of CQ was nearly uniform, however, the dose of schedule of HCQ varied widely among the included studies (except one large study, the cumulative dose in remaining of the studies was equal to or higher than the recommended). The median time from onset of symptom to admission or treatment initiation was nearly ≤8 days in all but 2 studies. Except one study, others

Table 1: Characteristics of included studies

Study author, Country[Ref]	Number of patients	Age (year) of patients (Mean±SD)	Disease severity	Dose schedule of CQ/HCQ	Time from symptom onset to treatment (d)	Additional information
Clinical trials (RCTs, and Non-RCTs)						
Gautret 2020, France[4]	N: 36 (HCQ=14; HCQ + AZM=6; Control=16)	HCQ=51.2±18.7; Control=37.3±24	All severity included Asymptomatic: 16.7% URTI: 61.1% LRTI: 22.2%.	HCQ: 600 mg/d (200 mg TID) for 10 days HCQ+AZM: AZM 500mg on day 1 followed by 250 mg OD for 4 days in addition to HCQ.	Mean±SD: 4.1±2.6 in HCQ group, and 3.9±2.8 in Control group	HCQ group recruited in one centre and control group in another. Attrition rate 23% in HCQ group. Funded study. There were protocol deviations.
Chen 2020, China[15]	N: 30 (HCQ=15; Control=15)	HCQ=50.5±3.8; Control=46.7±3.6	Not defined.	HCQ: 400 mg/d (OD) for 5 days.	Not mentioned	Major co-morbidities: hypertension (27%), diabetes (7%), and chronic obstructive lung disease (3.5%). Started enrolment 1 day prior to trial registration. Funded study
Tang 2020, China[16]	N: 150 (HCQ=75; Control=75)	HCQ=48.0±14.1; Control=44.1±15.0	Mild: 14.7% Moderate: 84% Severe: 1.3%	HCQ: 1200 mg/d for 3 days followed by 800 mg/d for the remaining days (total treatment duration: 2 weeks for mild/moderate, and 3 weeks for severe cases)	Mean: 16.6 (HCQ started within 24 h of randomization)	Trial stopped early. Major co-morbidities (30%): diabetes (14%), and others (20.7%). Funded study. Shanghai Pharma donated HCQ
Huang 2020, China[17]	N: 22 (CQ=10; Control=12)	CQ (median, IQR)=41.5 (33.8-50); Control (median, IQR)=53 (41.8-63.5)	Moderate: n64% Severe: 36%	CQ: 1000 mg/d (500 mg BID) for 10 days	Median: 2.5 in CQ group, and 6.5 in Control group	Underlying co-morbidities: hypertension (18.2%), diabetes (9.1%), and cerebro-vascular disease (4.5%). No protocol deviation. Funding status not mentioned
Borba 2020, Brazil[18]	N: 81 (CQ high-dose=41; CQ low-dose=40)	CQ high-dose=54.7±13.7; CQ low-dose=47.4±13.3	Severe: 89% (33% were critical)	High-dose CQ: 600mg BID for 10 days (total dose 12 g) Low-dose CQ: 450mg BID on day 1 followed by OD for 4 days (total dose 2.7 g)		Major co-morbidities: hypertension (45.5%), alcohol disorder (27.5%), and diabetes (25.5%). Older and more heart disease in the high-dose group. Funded study
Observational studies						
Huang 2020, China[19]	N: 373 (CQ=197; Control=176)	median (IQR): [CQ=43 (33-55); Control=47.5 (35.8-56)]	Mid: 3.8% Moderate: 91.4% Severe: 4.8%	CQ: 500 mg/d to 1000 mg/d (OD or BID) for 10 days	Median (IQR): 7 (3-10.8) after admission (Guangdong province). Median (IQR): 19 (17-124.5) after admission (Hubei province)	Major co-morbidities: hypertension (6.4%), diabetes (2.4%). Funded study
Mallat 2020, UAE[20]	N: 34 (HCQ=23; Control=11)	median (IQR): [HCQ=33 (31-48); Control=41 (30-55)]	Mild and moderate (100%)	HCQ: 800 mg/d (400 mg BID) on day 1 400 mg/d for 10 days	Median: 4 (HCQ started within 24 h)	Major co-morbidities: hypertension (14.7%), asthma (8.8%), and diabetes (5.9%).

HCQ: Hydroxychloroquine, CQ: Chloroquine, AZM: Azithromycin, RT-PCR: Reverse transcription polymerase chain reaction, URTI: Upper respiratory tract infection, LRTI: Lower respiratory tract infection, IQR: Inter-quartile range, ICU: Intensive care unit, OD: Once daily, BID: Twice daily, RCT: Randomised controlled trial, SD: Standard deviation

used CQ/HCQ within 48 h of admission/hospitalization. This might be due to the fact that starting anti-viral drugs (including HCQ/CQ) after 48 h of symptom onset might not be beneficial as the golden window for antiviral treatment (e.g. in influenza) is lost. However, this is difficult in a hospitalised setting (may be possible in outpatient or community setting). Another important point is that, the patients included in the present study were having comorbidities, and were on multiple drugs. The interactions between these drugs, and CQ/HCQ in affecting the action of the later on COVID-19 are unknown at present. Moreover, as none of the studies measured the blood level of these drugs, it is difficult to conclude this (at least to some extent). In two studies, recurrent COVID-19

Table 2: Characteristics of studies published in pre-print server (not peer-reviewed)

Study author[Ref]	Country	Study design	Number of participants (disease severity)	Dose schedule of CQ/HCQ	Viral outcome measures
Chen 2020[21]	China	RCT	62 (nonsevere cases)	HCQ 200 mg BID for 5 days	None
Chen 2020[22]	China	Observational study	284 (all severity)	CQ for 7 days	CQ does not enhance viral clearance
Feng 2020[23]	China	Observational study	50 (all severity)	CQ for 7 days	Chloroquine deserves further investigation
Shabrawishi 2020[24]	Saudi-Arabia	Observational study	93 (mild and moderate cases)	Group 1: CQ/HCQ Group 2: CQ/HCQ + azithromycin Group 3: CQ/HCQ + antiviral drugs	CQ/HCQ does not enhance virological cure

CQ: Chloroquine, HCQ: Hydroxy-chloroquine, RCT: Randomised controlled trial

Table 3: Outcome measures from clinical trials (randomised, quazi-randomised and nonrandomised)

HCQ/CQ versus control

Outcome measures	Number of trial (reference)	Sample size	Effect estimate	*P*
Time to negative COVID-19 RT-PCR (d)	2[14,15]	180	MD 1.55; 95% CI 0.7-3.79 (I^2=0%)	0.18
Proportion with negative COVID-19 RT-PCR				
After day 3	2[13,15]	180	OR 1.02; 95% CI 0.16-6.6 (I^2=78%)	0.98
After day 5	1[13]	30	OR 9.33; 95% CI 1.51-57.65	0.02*
After day 7	3[14-16]	202	OR 0.65; 95% CI 0.36-1.17 (I^2=0%)	0.15
After day 10	1[15]	150	OR 0.73; 95% CI 0.37-1.47	0.38
After day 14	3[14-16]	202	OR 0.98; 95% CI 0.44-2.15 (I^2=0%)	0.95
After day 21	1[15]	150	OR 1.49; 95% CI 0.62-3.61	0.37
After day 28	1[15]	150	Not pooled (event NE in HCQ group)	

HCQ and AZM versus control

Outcome measures	Number of trial (reference)	Sample size	Effect estimate	*P*
Proportion of patients with negative RT-PCR				
After day 3	1[13]	22	OR 15.0; 95% CI 1.32-169.89	0.03*
After day 5	1[13]	22	OR 0.45; 95% CI 0.02-10.67	0.62

High-dose versus low-dose CQ

Outcome measures	Number of trial (reference)	Sample size	Effect estimate	*P*
Proportion of patients with negative RT-PCR				
After day 3	1[13]	27	No separate data (6 patients negative)	NE

*P<0.05 significant. OR: Odds ratio, MD: Mean difference, CI: Confidence interval, RT-PCR: Reverse transcription polymerase chain reaction, Heterogeneity: I^2, AZM: Azithromycin, NE: Not estimable, CQ: Chloroquine, HCQ: Hydroxy-chloroquine

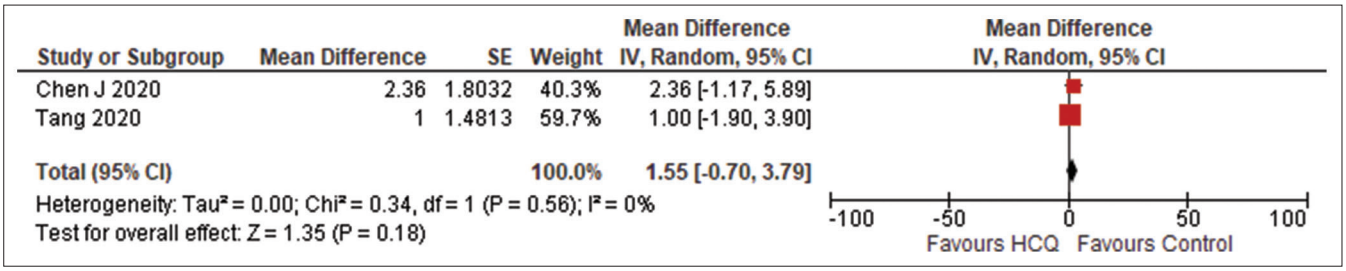

Figure 2: Time to virological cure (hydroxychloroquine vs. control; result from randomised controlled trials)

infection was noted (from faecal samples in one study). The authors could not explain the reason for the same as none of the patients in the control group was positive. Future studies with larger samples might provide insight into the causation.

Limitations

The studies were variable in many aspects (blinding of participants and outcome assessors, patient selection, severity of illness, dose schedule of the anti-malarial drugs, timing of

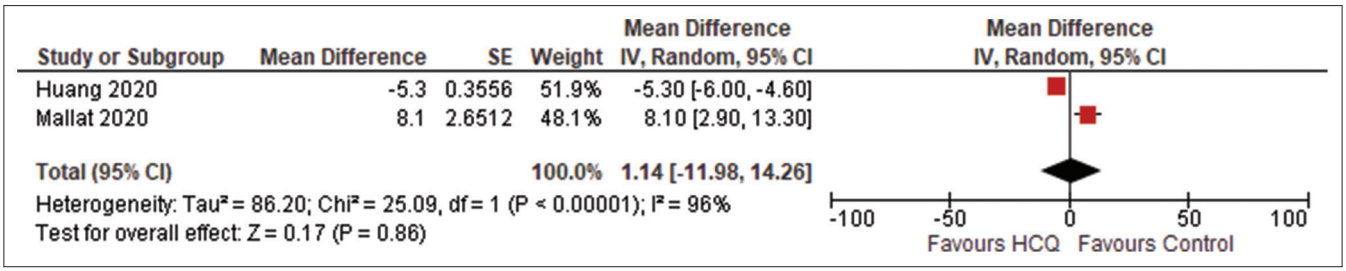

Figure 3: Time to virological cure (hydroxychloroquine vs. control; result from observational studies)

Table 4: Outcome measures from observational studies

HCQ or CQ versus control				
Outcome measures	**Number of study (reference)**	**Sample size**	**Effect estimate**	***P***
Time to negative PCR results for COVID-19 (days)	2[23,25]	407	MD 1.14; 95% CI -11.98-14.26 (I^2=89%)	0.86
Proportion of patients with negative COVID-19 PCR				
After day 10	1[25]	373	OR 7.86; 95% CI 4.4-14.04	<0.001*
After day 14	2[23,25]	407	OR 6.37; 95% CI 3.01-13.48 (I^2=0%)	<0.001*

**P*<0.05 significant. OR: Odds ratio, MD: Mean difference, CI: Confidence interval, PCR: Polymerase chain reaction, Heterogeneity: I^2, CQ: Chloroquine, HCQ: Hydroxy-chloroquine

Table 5: GRADE evidence (Effect of Chloroquine/Hydroxy-chloroquine±Azithromycin vs. Standard of care on COVID-19 virological outcomes)

Outcomes	Number of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects*	
				Risk with Standard of care	Risk difference with Anti-malarial drugs (95% CI)
Primary outcome measures					
Time to virological cure (d)	180 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b,c] due to risk of bias, imprecision	MD 1.55 (-0.7 to 3.79)	The mean time to virological cure (d) in the intervention groups was 1.55 higher (0.7 lower to 3.79 higher)	
Time to virological cure (d)	407 (2 observational studies)	⊕⊖⊖⊖ Very low[b,d,e] due to risk of bias, inconsistency, imprecision, publication bias	MD 1.14 (-11.98 to 14.26)	The mean time to virological cure (d) in the intervention groups was 1.14 higher (11.98 lower to 14.26 higher)	
Secondary outcome measures**					
Proportion of patients with virological cure after day 3	180 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b,c,e] due to risk of bias, inconsistency, imprecision, publication bias	OR 1.02 (0.16 to 6.6)	Study population 657 per 1000	102 fewer per 1000 (from 249 fewer to 34 more)
Proportion of patients with virological cure after day 7	202 (3 RCTs)	⊕⊖⊖⊖ Very low[a,f] due to risk of bias, imprecision	OR 0.65 (0.36 to 1.17)	Study population 187 per 1000	241 more per 1000 (from 69 more to 433 more)
Proportion of patients with virological cure after day 14	202 (3 RCTs)	⊕⊖⊖⊖ Very low[a,d,g] due to risk of bias, inconsistency, imprecision	OR 0.98 (0.44 to 2.15)	Study population 853 per 1000	3 fewer per 1000 (from 134 fewer to 73 more)
Proportion of patients with virological cure after day 14	407 (2 observational studies)	⊕⊖⊖⊖ Very low[b,d,e] due to risk of bias, publication bias	OR 6.37 (3.01 to 13.48)	Study population 802 per 1000	161 more per 1000 (from 122 more to 180 more)

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI), **Secondary outcomes: pooled results from minimum 2 studies are reported here. GRADE Working Group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect, Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate, Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate, Very low quality: We are very uncertain about the estimate. [a]Open label trials with difference in the dose schedule of intervention and time to start of intervention, [b]Sample size was less with wider 95% CI that includes line of no effect, [c]The results from both the studies were contradictory, [d]Case-control studies, [e]One study was small with very significant cure rate, [f]95% was wider, [g]In one trial, all patients in both the groups were cured. CI: Confidence interval; OR: Odds ratio; MD: Mean difference, RCT: Randomised controlled trial

administration, etc). Due to lack of paediatric data, the results of present review cannot be extrapolated to this population.

Conclusions

CQ/HCQ does not affect the time to virological cure compared to usual/standard of care used in the treatment of COVID-19 infection at present. Recurrent infection in a smaller number of patients was noted in the CQ/HCQ group. Good quality and multi-centric RCTs are required for any firm conclusion to be drawn or recommendation to be made during the on-going pandemic.

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Conflicts of interest

There are no conflicts of interest.

References

1. Wu Z, McGoogan JM. Characteristics of and important lessons from thecoronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese center for disease control and prevention. JAMA 2020; 10.1001/jama.2020.2648.[published online ahead of print, 2020 Feb 24].
2. COVID-19 in India. Available from: https://www.mohfw.gov.in/. [Last accessed on 2020 June 15].
3. Saber-Ayad M, Saleh MA, Abu-Gharbieh E. The rationale for potential pharmacotherapy of COVID-19. Pharmaceuticals (Basel) 2020;13: 96.
4. Gautret P, Lagier JC, 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; 56:105949.
5. Das RR, Jaiswal N, Dev N, Jaiswal N, Naik SS, Sankar J. Efficacy & safety of anti-malarial drugs (Chloroquine, and Hydroxy-chloroquine) in treatment of COVID-19 infection: A systematic review & meta-analysis. Front Med 2020; 7:482.
6. Keyaerts E, Li S, Vijgen L, Rysman E, Verbeeck J, Ranst MV, *et al*. Antiviral activity of chloroquine against human coronavirus OC43 infection in newborn mice. Antimicrob Agents Chemother 2009;53:3416-21.
7. 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;2:69.
8. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS coronavirus. J Virol 2020;94: e00127-20.
9. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, *et al*. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270-3.
10. Devaux CA, Rolain JM, 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;55: 105938.
11. Golden EB, Cho HY, Hofman FM, Louie SG, Schönthal AH, Chen TC. Quinoline-based antimalarial drugs: A novel class of autophagy inhibitors. Neurosurg Focus 2015;38:E12.
12. Gbinigie K, Frie K. Should chloroquine and hydroxychloroquine be used to treat COVID-19? A rapid review. BJGP Open 2020;4: bjgpopen20X101069.
13. 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 2020; 71:732-9.
14. Sahraei Z, Shabani M, Shokouhi S, Saffaei A. Aminoquinolines against coronavirus disease 2019 (COVID-19): Chloroquine or hydroxychloroquine. Int J Antimicrob Agents 2020;55:105945.
15. Chen J, Liu D, Liu L, Liu P, Xu Q, Xia L, *et al*. A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. Zhejiang Da Xue Xue Bao Yi Xue Ban 2020;49:215-9.
16. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, *et al*. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: Open label, randomised controlled trial. BMJ 2020;369:m1849.
17. Huang M, Tang T, Pang P, Li M, Ma R, Lu J, *et al*. Treating COVID-19 with Chloroquine. J Mol Cell Biol 2020;12:322-5.
18. Borba M, de Almeida Val F, Sampaio VS, Alexandre MAA, Melo GC, Brito M, *et al*. Effect of high vs. low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: A randomized clinical trial. JAMA Netw Open 2020;3:e208857.
19. Huang M, Li M, Xiao F, Pang P, Liang J, Tang T, *et al*. Preliminary evidence from a multicenter prospective observational study of the safety and efficacy of chloroquine for the treatment of COVID-19. Natl Sci Rev 2020; nwaa113.
20. 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. medRxiv 2020.04.27.20082180;doi:https://doi.org/10.1101/2020.04.27.20082180.
21. 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. medRxiv 2020.03.22.20040758;doi: https://doi.org/10.1101/2020.03.22.20040758.
22. Chen X, Zhang Y, Zhu B, Zeng J, Hong W, He X, *et al*. Associations of clinical characteristics and antiviral drugs with viral RNA clearance in patients with COVID-19 in Guangzhou, China: A retrospective cohort study. medRxiv 2020.04.09.20058941;doi: https://doi.org/10.1101/2020.04.09.20058941.
23. Feng Z, Li J, Yao S, Yu Q, Zhou W, Mao Z, *et al*. The use of adjuvant therapy in preventing progression to severe pneumonia in patients with coronavirus disease 2019: A multicenter data analysis. medRxiv 2020; medRxiv 2020.04.08.20057539;doi: https://doi.org/10.1101/2020.04.08.20057539.
24. Shabrawishi MH, Naser AY, Alwafi H, Aldobyany AM, Touman AA. Negative nasopharyngeal SARS-CoV-2 PCR conversion in Response to different therapeutic interventions. medRxiv 2020; medRxiv 2020.05.08.20095679; doi: https://doi.org/10.1101/2020.05.08.20095679.
25. 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;92:776-85.
26. China National Health Commission. Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition), updated on; 16 March 2020. Available from: http://kjfy.meetingchina.org/msite/news/show/cn/3337.html. [Last accessed 2020 Jun 14].
27. Higgins JP, Altman DG, Gøtzsche PC, Juni P, Moher D, Oxman AD, *et al*. The cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:D5928.
28. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, *et al*. The Newcastle Ottawa scale (NOS) for assessing the Quality of Nonrandomised Studies in Meta-Analysis. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxfordasp. [Last accessed on 2020 Apr 22].
29. Sterne JA, Hernán MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, *et al*. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:I4919.
30. Review Manager (RevMan) Computer program. Ver. 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014. [Last accessed on 2020 Apr 22] https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman.

31. Schmidt FL, Oh IS, Hayes TL. Fixed- versus random-effects models in meta-analysis: Model properties and an empirical comparison of differences in results. Br J Math Stat Psychol 2009;62:97-128.
32. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0. The Cochrane Collaboration; 2008. Available from: http://www.cochrane-handbook.org. [Last accessed on 2020 Jun 14].
33. GRADEpro GDT: GRADEpro Guideline Development Tool Software. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from: http://gradepro.org. [Last accessed 0n 2020 Apr 22].
34. Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations. Updated October 2013. The GRADE Working Group; 2013. Available from: http://guidelinedevelopment.org/handbook. [Last accessed 2020 Apr 22].
35. Harper SA, Bradley JS, Englund JA, File TM, Gravenstein S, Hayden FG, *et al*. Expert Panel of the Infectious Diseases Society of America. Seasonal influenza in adults and children–diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: Clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2009;48:1003-32.
36. Touret F, de Lamballerie X. Of chloroquine and COVID-19. Antiviral Res 2020;177: 104762.