Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Update I. A systematic review on the efficacy and safety of chloroquine/hydroxychloroquine for COVID-19

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ABSTRACT

Purpose: To assess efficacy and safety of chloroquine (CQ)/hydroxychloroquine (HCQ) for treatment or prophylaxis of COVID-19 in adult humans.
Materials and methods: MEDLINE, PubMed, EMBASE and two pre-print repositories (bioRxiv, medRxiv) were searched from inception to 8th June 2020 for RCTs and nonrandomized studies (retrospective and prospective, including single-arm, studies) addressing the use of CQ/HCQ in any dose or combination for COVID-19.
Results: Thirty-two studies were included (6 RCTs, 26 nonrandomized, 29,192 participants). Two RCTs had high risk, two 'some concerns' and two low risk of bias (Rob2). Among nonrandomized studies with comparators, nine had high risk and five moderate risk of bias (ROBINS-I). Data synthesis was not possible. Low and moderate risk of bias studies suggest that treatment of hospitalized COVID-19 with CQ/HCQ may not reduce risk of death, compared to standard care. High dose regimens or combination with macrolides may be associated with harm. Post-exposure prophylaxis may not reduce the rate of infection but the quality of the evidence is low.
Conclusions: Patients with COVID-19 should be treated with CQ/HCQ only if monitored and within the context of high quality RCTs. High quality data about efficacy/safety are urgently needed.

1. Introduction

The spread of the coronavirus disease 2019 (COVID-19) caused by the novel SARS-CoV-2 has reached pandemic dimensions. Many drugs, both repurposed and new, have and are being investigated for preventing or treating the disease [1,2]. Chloroquine (CQ) and its related formulations (e.g. hydroxychloroquine – HCQ) were introduced at a very early stage of the pandemic as a potential treatment for COVID-19. At the time, only pre-clinical rationale, in vitro findings and meager animal model data were available [3]. The desperate need for an effective treatment has led to widespread use of the drug nonetheless. Dependent on location, CQ/HCQ are being used in the context of clinical trials or as standard care.

As the pandemic evolves, the amount of evidence accumulated regarding various treatment options is growing rapidly. However, the efficacy and safety of CQ/HCQ remains unclear [4]. We therefore aimed to systematically search, assess and summarize the existing literature related to the efficacy and safety of these drugs in the clinical context of treatment and prophylaxis of COVID-19. We also set out to pool and meta-analyze the most updated data, if possible, in order to ascertain whether any conclusions can be reached at this time regarding the association between CQ/HCQ and hospital mortality in patients with COVID-19 or disease prevention in those exposed.

2. Materials and methods

We prospectively registered the protocol of this review on Open Science Framework (OSF) on 12th May 2020 (osf.io/3yka8).

2.1. PICO question

The current review covers studies comparing adult patients with or at risk of COVID-19 (P) who had been administered CQ or related formulations, alone or in combination with other drugs (I) to those given standard care or other regimens or drugs (C). The outcomes of interest

Abbreviations: CI, Confidence interval;; COVID-19, Coronavirus disease 2019;; CQ, Chloroquine;; ECG, Electrocardiogram;; HCQ, Hydroxychloroquine;; HCWs, Healthcare workers;; HR, Hazard Ratio;; ICU, Intensive care unit;; RCT, Randomized clinical trial; Rob2, Revised tool for Risk of Bias in randomized trials;; ROBINS-I, Risk of Bias in Non-randomized Studies of Interventions;; RR, Risk Ratio; NOS, Newcastle Ottawa Scale;; WHO, World Health Organization.

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were both efficacy (i.e. mortality, viral clearance, infection rate) and safety (i.e. adverse events, focusing on cardiac events) (O).

2.2. Search strategy

The search strategy is presented in full in Supplementary Material 1. In brief, we performed a comprehensive search of MEDLINE, PubMed and EMBASE from inception to 8th June 2020 for both randomized and nonrandomized studies, both retrospective and prospective [5] addressing the PICO question. We did not apply any language or quality restrictions. Following full-text download (see below) the reference lists of relevant articles were also screened (i.e. snowballing method). Two major pre-print servers (bioRxiv and medRxiv) were also searched for relevant not peer-reviewed articles from inception to 8th June 2020.

2.3. Study inclusion and exclusion process

Studies were selected for inclusion using a two-stage process. First, the publications listed in the full literature search were screened independently by two investigators (AC, MI) to identify all potentially relevant publications based on their titles and abstracts. Then the full-text manuscripts of the publications selected were retrieved and assessed by two investigators (MI, GI) against the predetermined inclusion criteria. Disagreement over study inclusion was resolved by consensus or, if necessary, by arbitration by other authors (AG, SE). For comprehensiveness, we decided to include also relevant single-arm studies without a comparison group. We excluded articles reporting data with complete or partial overlap with other reports. Abstracts, conference proceedings, and publications describing a single treatment arm were included only if they presented sufficient details to allow assessment of both the methods and the results.

2.4. Assessment of risk of bias (RoB)

Two of the authors (AC, MI) assessed the RoB of the included studies independently and in duplicate. Disagreements over RoB were resolved by consensus or, if necessary, adjudicated by a third author (SE). The Rob2 tool (Revised tool for Risk of Bias in randomized trials) was used for assessing randomized trials [6]. The ROBINS-I tool (Risk Of Bias in Non-randomized Studies of Interventions) was used for RoB of nonrandomized studies with comparison between relevant study groups [7]. The Newcastle Ottawa Scale (NOS) was used for assessing single-arm nonrandomized studies, without evaluating the "comparability" item [8]. For each domain we rated the overall RoB as the highest risk attributed to any criterion. We used the Robvis tool (visualization tool for risk of bias assessments in a systematic review) [9] for presenting the data as appropriate. The final RoB assessments are reported as either a plot or a table as per requirement (see below).

2.5. Data collection and management

The primary study outcomes were all-cause mortality at the longest reported follow-up for studies evaluating CQ/HCQ as treatment, and infection rate in prophylactic studies. Two authors (AC, MI) extracted information regarding study design, sample size, patients' characteristics, interventions and outcomes using a pre-piloted data extraction form in duplicate. If important data were missing or remained unpublished in any of the relevant studies, the authors were contacted by one of the reviewers with the aim of retrieving this data. The extracted data were used for both the description of the included studies and the qualitative analysis.

2.6. Measures of treatment effect

Our protocol specified that quantitative synthesis would be performed only if two or more studies were identified with sufficient homogeneity in study design, interventions and outcomes and low risk of bias [10].

3. Results

The qualitative analysis included a total of 32 studies (29,192 participants) selected from the 5711 screened records from MEDLINE, PubMed and EMBASE databases, pre-print servers and other sources. The inclusion/exclusion process is detailed in a supplementary flow-diagram (Supplementary Material 2) and the PRISMA checklist is reported in the Supplementary Material 3.

3.1. Characteristics of the included studies

Among the included studies, 6 were RCTs and 26 were nonrandomized studies. Nine of the studies were found in pre-print repositories and were not peer reviewed at the time of their inclusion in this review. The characteristics and the main findings of the included studies are provided in Table 1.

3.2. Studies with a "no CQ/HCQ" control group

Chen et al. conducted an open label randomized trial in one centre in China, enrolling 30 patients with confirmed COVID-19 after informed consent. Patients were randomized to receive HCQ (400 mgX1/day) or standard care. No significant differences were detected between the groups in the rates of negative throat swabs for viral nucleic acid at day 7 (primary outcome) or in the rates of clinical worsening, adverse events and death at day 14 [11].

Geleris et al. conducted a single-centre nonrandomized study in New York City, enrolling 1376 consecutive adult hospitalized patients with a positive PCR test for SARS-CoV-2 [12]. The authors excluded patients who were intubated, died, or discharged within 24 h after presentation to the emergency department. Patients receiving HCQ were compared to those not receiving HCQ. The primary endpoint was time from study baseline to intubation or death (composite outcome). Within the study follow-up period, 346 patients (25.1%) had a primary end-point event but among these almost half ($n = 166$) died without being intubated. Unadjusted analysis suggested an association between HCQ use and a higher risk of occurrence of primary outcome events (hazard ratio - HR 2.37; 95% CI,1.84 to 3.02). However, those receiving HCQ were more severely hypoxemic ill at baseline. Neither adjusted multivariable analysis (HR 1.00; 95% CI, 0.76–1.32) nor propensity score analysis with inverse probability weighting (HR 1.04; 95% CI, 0.82 to 1.32) confirmed the presence of increased risk. Azithromycin was given to 44.5% (613/1376) of the whole cohort and to 54.2% (588/1085) of the propensity-score matched cohort. No association was found between the use of azithromycin and the primary outcome.

Huang et al. conducted a small, unblinded RCT in one centre in China, enrolling 22 patients with confirmed COVID-19 to treatment with CQ or lopinavir/ritonavir [13]. Patients receiving CQ had more rapid conversion of RT-PCR to negative and resolution of computed tomography findings and all treated patients were discharged home by day 14 compared to only half of those receiving lopinavir/ritonavir. In the CQ group, five patients experienced nine gastrointestinal, pulmonary and dermatological adverse events.

Mahevas et al. studied 173 patients with SARS-CoV-2 pneumonia that required ≥2 L/min oxygen in four hospitals. Among these, 84 received HCQ within 48 h of admission (not randomized) [14]. Weighted comparison showed that patients with and without HCQ treatment had similar rates of ICU admission or death at day 21 (76% in the treatment group vs. 75% in the control group; weighted hazard ratio 0.9, 95% C·I 0.4–2.1). Survival without ARDS at day 21 was 69% in the treatment group compared with 74% in the control group (HR 1.3, 0.7–2.6). Treatment with HCQ was discontinued in eight patients (10%) for ECG alterations.

Table 1
Characteristics of the included studies

Author [Ref.]	ID	Country	Design	Participants (*n*)	Treatment	Comparison	Outcomes[a]	Results[b]	Risk of Bias (tool)[c]
Studies with a "no CQ/HCQ" control group									
Chen et al. [11]	NCT04261517	China	Single-centre RCT	Patients with COVID-19 ($n = 30$)	HCQ sulphate 400 mg, oral formulation, daily for 5 days ($n = 15$)	Standard care ($n = 15$)	Negative conversion rate of SARS-CoV-2 nucleic acid in respiratory pharyngeal swab at day 7 or death at day 14; adverse events	Negative nucleic acid negative in 86.7% of the HCQ group and 93.3% of the control group ($P > 0{,}05$). No deaths at last follow-up. Averse events in 26.7% of the HCQ group and 20% of the control group ($p > .05$)	High risk of bias (Rob2)
Geleris et al. [12]	NA	USA	Single-centre prospective observational study	Hospitalized patients with COVID-19 ($n = 1376$)	HCQ 600 mg twice on day 1, then 400 mg daily for 4 days; with or without AZ 500 mg on day 1 and then 250 mg daily for 4 more days ($n = 811$)	Treatment regimens not including HCQ ($n = 565$)	Time to intubation or death	HCQ group: higher risk of primary outcome (hazard ratio - HR 2.37; 95% CI,1.84 to 3.02). Findings not confirmed by neither multivariate analysis (HR 1.00; 95% CI, 0.76–1.32) nor propensity score analyses (HR 1.04; 95% CI, 0.82 to 1.32). No association between AZ use and primary outcome (HR 1.03; 95% CI, 0.81 to 1.31).	Moderate risk of bias (ROBINS-I tool)
Huang et al. [13]	NA	China	Single-centre RCT	Hospitalized patients with confirmed COVID-19 ($n = 22$)	CQ 500 mg orally twice daily for 10 days ($n = 10$)	Lopinavir/Ritonavir 400 mg/100 mg twice daily for ten days ($n = 12$)	Viral clearance; improvements on lung CT; length of hospitalization; adverse events	Discharge at day 14 was registered for 100% of the patients in the CQ group vs the 50% of the Lopinavir/ Ritonavir group. Five patients experienced a total of 9 adverse events in the CQ group.	High risk of bias (Rob2)
Mahevas et al. [14]	NA	France	Multicentre nonrandomized prospective study	Hospitalized patients with COVID-19 ($n = 173$)	HCQ 600 mg daily, started in the first 48 h after hospitalization ($n = 84$)	No HCQ in the first 48 h ($n = 89$)	Survival without transfer to the ICU at day 21; QT	Survival rate without transfer to the ICU at day 21 was 76% in the treatment group and 75% in the control group (weighted hazard ratio 0.9, 95% confidence interval 0.4 to 2.1; Eight (10%) of the HCQ group experienced electrocardiographic modifications requiring discontinuation.	Moderate risk of bias (ROBINS-I)
Rosenberg et al. [15]	NA	USA	Multicentre retrospective observational study	Hospitalized patients with COVID-19 ($n = 1438$)	HCQ alone (most common dosage 400 mg first dose then 200 mg daily); HCQ in combination with AZ; AZ alone (most common dosage 500 mg daily) ($n = 1217$)	Treatment regimens not including HCQ or AZ ($n = 221$)	In-hospital mortality; adverse events	The HCQ + AZ group had the highest in-hospital mortality (25.7%). No significant differences in mortality between HCQ + AZ (aHR, 1.35 [95% CI, 0.76–2.40]), HCQ alone (aHR, 1.08 [95% CI, 0.63–1.85]), or AZ alone (aHR, 0.56 [95% CI, 0.26–1.21]), compared with neither drug in the adjusted analysis. Cardiac arrest more likely in HCQ + AZ than neither drug (aOR, 2.13 95% CI, 1.12–4.05), and in HCQ alone vs AZ alone (aOR, 2.97 95% CI, 1.56–5.64)	Moderate risk of bias (ROBINS-I)
Tang et al. [16]	ChiCTR2000029868	China	Multicentre RCT	Hospitalized patients with	HCQ 1200 mg daily for 3 days, then 800 mg daily for the	Standard care ($n = 75$)	Negative conversion of SARS–CoV–2 at	Similar median time to negative conversion in HCQ group (8 (95%	Some concerns

				confirmed COVID–19 ($n = 150$)	remaining days (total treatment duration: 2–3 weeks) ($n = 75$)		day 28; adverse events	confidence interval 5 to 10) days) vs standard care group (7 (5 to 8) days) (hazard ratio 0.85, 95% C·I 0.58–1.23; $P = .34$ by log rank test). Adverse events in 9% of HCQ non–recipients vs 30% of HCQ recipients.	(Rob2)
Yu et al. [17]	NA	China	Single-centre retrospective observational study	Critically ill patients with COVID-19 ($n = 550$)	HCQ 200 mg twice daily for 7–10 days ($n = 48$)	Standard care ($n = 502$)	Mortality; hospital length of stay; level of IL-6	HCQ associated with a significantly decreased fatality risk (HR: 0.31; 95% CI: 0.16–0.61; $P = .001$; adjusted HR: 0.36; 95% CI: 0.18–0.75; $P = .006$). The time of hospital stay before patient death was lower for the HCQ group, compared to NHCQ group ($P < .05$). The levels of IL-6 were significantly reduced in the HCQ group.	Serious risk of bias (ROBINS-I)
Studies without a "no CQ/HCQ" comparison group									
Borba et al. [18]	NCT04323527	Brazil	Single-centre parallel,double--masked,-randomized,-phaseIIb clinical trial	Hospitalized patients with severe acute respiratory syndrome and suspected diagnosis of COVID-19 ($n = 81$)	CQ 600 mg (four tablets containing 150 mg CQ base) twice daily for 10 days ($n = 41$)	Day 0: CQ 450 mg (three tablets containing 150 mg CQ base) and 1 placebo tablet twice daily; Day 1 to day 4: 450 mg (three tablets containing 150 mg) plus 1 placebo tablet once a day followed by 4 placebo tablets once daily; Day 5 to day 9: four placebo tablets twice daily ($n = 40$)	Reduction in lethality at day 28 by at least 50% in the high-dosage group compared with the low-dosage group; adverse events	Lethality until day 13 in 39% of high-dosage group vs. 15% of low-dosage group. QTc > 500 milliseconds in 18.9% of the high-dosage group vs. 11.1% of low-dosage group. Ventricular tachycardia in 2.7% of the high-dosage group experienced ventricular tachycardia. CK increase in 50.0% of high-dosage group vs 31.6% of low-dosage group. The high-dosage group was associated with lethality (odds ratio, 3.6; 95% CI, 1.2–10.6).	Low risk of bias (Rob2)
Gautret et al. [20]	NA	France	Single-centre single arm retrospective observational study	Patients with positive PCR test for SARS-CoV-2 ($n = 80$)	HCQ 200 mg, three times daily for 10 days and AZ 500 mg on day and 250 mg daily for the next 4 days	No comparison	Clinical outcome; ICU admission at day 3; results of PCR and cultures; length of stay	The 81.3% of the patients had favourable outcome and were discharged, 15% required oxygen therapy, 93% had negative viral load at day 8	Poor quality score (NOS)
Million et al. [19]	NA	France	Single-centre single arm retrospective observational study	Patients with positive PCR test for SARS-CoV-2, both admitted in day-care or conventional unit. ($n = 1061$)	HCQ 200 mg 3 times daily for 10 days and AZ 500 mg on day 1 and 250 daily for 4 days	No comparison	Clinical outcome; ICU admission or death; hospitalization ≥10 days; results of PCR and cultures; adverse events	Good clinical outcome and virological cure were achieved in 91.7% of patients at day 10. Adverse events occurred in 2.4% of the patients.	Poor quality score (NOS)
Molina et al. [21]	NA	France	Single-centre rospective observational study	Hospitalized patients for COVID-19 ($n = 11$)	HCQ 600 mg daily for 10 days and AZ 500 mg on day 1 and 250 mg daily from day 2 to day 5	No comparison	Virological clearance; clinical outcome; prolonged QTc; adverse events	In one patient, HCQ and AZ were discontinued after 4 days because of a prolongation of the QT interval.	Poor quality score (NOS)
Studies addressing cardiac adverse events only									
Bessiere et al. [26]	NA	France	Single-centre, retrospective, observational study	Patients admitted in ICU for COVID-19 (n = 40)	HCQ 200 mg, twice a day, for 10 days, with or without AZ 250 mg, daily, for 5 days	No comparison	Prolonged QTc; ΔQTc; adverse events	Prolonged QTc was observed in 14 patients (36%). Median ΔQTc was 35 (10–66). The treatment was ceased in 17.5% of the	Poor quality score (NOS)

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Table 1 (*continued*)

Author [Ref.]	ID	Country	Design	Participants (n)	Treatment	Comparison	Outcomes[a]	Results[b]	Risk of Bias (tool)[c]
								patients following ECG abnormalities and in the 25% of the patients for acute renal failure.	
Chorin et al. [24]	NA	USA	Multicentre retrospective observational study	Hospitalized patients with COVID-19 ($n = 251$)	HCQ 400 mg twice daily on day 1, then 200 mg twice daily for 4 days and AZ 500 mg once daily for 5 days	No comparison	QTc prolongation	QTc > 500 ms in 28/222 (13%) patients with QRS < 120. JTc > 410 in 4/29 (14%) patients with QRS >120. ΔQTc>60 in 51/251 (20%) patients with any QRS	Poor quality score (NOS)
Maraj et al. [25]	NA	USA	Single-centre retrospective observational study	Hospitalized patients with COVID-19 ($n = 91$)	Hydroxychloroquine and azithromycin	No comparison	Significant QTc prolongation; ventricular tachyarrhythmias	Excessive QTc prolongation occurred in 23%. Significant ventricular arrhythmias occurred in 2 patients (1 classic TdP and 1 polymorphic VT degenerating into VF). Additional QT prolonging agents (especially propofol) independently associated with QTc prolongation [any drug: adjusted OR 3.69, CI (1.22, 11.20), $p = .02$; propofol: adjusted OR 3.28, CI (1.06, 10.17), $p = .04$].	Poor quality score (NOS)
Mazzanti et al. [22]	NA	Italy	Single-centre prospective observational study	Hospitalized patients with COVID-19 ($n = 150$)	HCQ for a median of 9 days (IQR 5–11), at a daily dosage of 400 mg (97%), or 600 mg (3%). In 67% of cases, HCQ with LopinavirRitonavir (35%), AZT (26%), or LR + AZT (6%)	No comparison	QTc prolongation	Median ΔQTc 18 ms (IQR 2–34 ms; $p < .001$; baseline QTc available only for 79 patients); 9% QTc mild prolongation; 4% intermediate and 2% severe (≥500 ms)	Poor quality score (NOS)
Mercuro et al. [23]	NA	USA	Single-centre, retrospective, observational study	Hospitalized patients with COVID-19 ($n = 90$)	HCQ 400 mg twice on day 1, then 400 mg once daily for 4 days ($n = 37$)	HCQ and azithromycin ($n = 53$)	ΔQTc; prolonged QTc; adverse events	Patients receiving HCQ alone had a median ΔQTc of 5.5 IQR −15.5–34.25) vs the 23 ms median (IQR 10–40) of HCQ and AZ group; $p = .03$. The 19% of HCQ alone group vs 21% of combination group developed QTc ≥ 500 ms. The 3% of HCQ alone group vs 13% of combination group had ΔQTc >60 ms. One patient developed torsades de pointes in the combination group.	Serious risk of bias (ROBINS-I)
Peng et al. [29]	NA	Malaysia	Single-centre nonrandomized observational study	Hospitalized patients with COVID-19 ($n = 13$)	HCQ with or without azithromycin	No comparison	Tisdale score and QTc prolongation	Mean Tisdale risk score 7.5 ± 1.45, with 69.2% at intermediate risk of QT prolongation. QT prolongation in 38.5% of the patients	Poor quality score (NOS)
Saleh et al. [28]	NA	USA	Multicentre prospective observational study	Hospitalized patients with COVID-19 ($n = 201$)	CQ: 500 mg oral twice daily at day1, followed by 500 mg once daily for 4 days; or HCQ: 400 mg oral twice daily at day 1 followed by 200 mg twice daily for 4 days; In combination with AZ 500 mg oral or i.v. daily for 5 days ($n = 119$)	CQ alone: 500 mg oral twice daily at day1, followed by 500 mg once daily for 4 days; HCQ alone: 400 mg oral twice daily at day 1 followed by 200 mg twice daily for 4 days ($n = 82$)	QT prolongation with torsades de pointes	No cases of torsades de pointes or arrhythmogenic death. Baseline QTc did not differ between monotherapy vs. combination group (440.6 ± 24.9 ms vs. 439.9 ± 24.7 ms, $p = .834$). QTc was significantly longer in the combination vs monotherapy group (470.4 ± 45.0 ms vs.	Serious risk of bias (ROBINS-I)

								453.3 ± 37.0 ms, $p = .004$). Seven patients (3.5%) required discontinuation due to QTc prolongation.	
Van den Broek et al. [27]	NA	The Netherlands	Single-centre retrospective observational study	Hospitalized patients suspected for COVID-19 ($n = 95$)	CQ loading dose 600 mg, followed by 300 mg twice daily (starting 12 h after the loading dose), for a total of 5 days	No comparison	ECG alterations, PR, QRS and QTc intervals	Mean QTc prolongation of 35 ms (95% CI 28–43 ms) using computerized interpretation and 34 ms (95% CI 25–43 ms) on manual interpretation; 23% of the patients had a QTc > 500 ms. Heart rate mean difference was −10 bpm, PR interval mean difference was 8 ms and QRS interval mean difference was 6 ms.	Poor quality score (NOS)
Studies on prophylactic use									
Boulware et al. [30]	NA	USA and Canada	Multicentre RCT	Asymptomatic non-hospitalized adults with high or moderate risk exposure to SARS-CoV-2 ($n = 821$)	HCQ 800 mg (4 tablets) once, then 600 mg (3 tablets) 6 to 8 h later, then 600 mg (3 tablets) daily for 4 days (5 days,19 tablets total) ($n = 414$)	Placebo ($n = 407$)	COVID-19 related symptoms	13.0% of the participants turned symptomatic by 14 days. Symptoms appearance did not differ significantly between those receiving HCQ (11.8%) and those receiving placebo (14.3%), $p = .35$	Low risk of bias (Rob-2)
Gendelman et al. [33]	NA	Israel	Multicentre retrospective observational study	Individuals tested for COVID-19 ($n = 14{,}520$)	HCQ regimens (in use prior to COVID-19 for other clinical reasons) ($n = 36$)	No HCQ regimens (n = 14,484)	SARS-CoV-2 infection rate	Hydroxychloroquine was prescribed to subjects with SARS-CoV-2 infection com- pared to those without in rate of 0.23% vs 0.25% ($p = .877$) of the population	Serious risk of bias (ROBINS-I)
Konig et al. [34]	NA	USA	Multicentre retrospective observational study	Patients with SLE and COVID-19 ($n = 80$)	HCQ or chloroquine (in use prior to COVID-19 for other clinical reasons) ($n = 51$)	No HCQ or chloroquine regimens ($n = 29$)	SARS-CoV-2 infection rate; hospitalization rate	Fifty-one (64%) patients were already using hydroxychloroquine or chloroquine before SARS-CoV-2 infection. Frequency of hospitalization did not significantly differ between antimalarial users versus non-users	Serious risk of bias (ROBINS-I)
Nagaraya et al. [32]	NA	India	Multicentre retrospective observational study	Healthcare workers in "direct contact"(66.9%), "indirect contact"(27.9%) or "no contact" (3.4%) with patients ($n = 166$)	HCQ	No comparison	Adverse events	At least one adverse event was experienced by 37.9% participants	Poor quality score (NOS)
Not peer reviewed, pre-print studies									
Ahmad et al. [43]	NA	USA	Multicentre retrospective observational study	Residents in long-term facilities with suspected or	Doxycycline 100 mg p.o. twice daily for 7 days and HCQ (200 mg p.o. three times daily for 7 days or 400 mg p.o. twice	No comparison	Clinical recovery	All patients improved within 6 days of DOXY-HCQ initiation. 93% ($n = 50$) did not display any side-effects of DOXY-HCQ. 2%	Poor quality score (NOS)

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Table 1 (*continued*)

Author [Ref.]	ID	Country	Design	Participants (n)	Treatment	Comparison	Outcomes[a]	Results[b]	Risk of Bias (tool)[c]
				confirmed COVID-19 ($n = 54$)	daily at day 1, then 400 mg daily for 6 days)			($n = 1$) had a seizure and HCQ was immediately terminated. 9 patients did not complete the 7-day course of DOXY-HCQ due to hospital transfers, death, or side-effects.	
Carlucci et al. [36]	NA	USA	Single-centre retrospective observational study	Hospitalized patients with confirmed SARS-CoV-2 infection ($n = 932$)	HCQ 400 mg load followed by 200 mg twice daily for five days, and AZ 500 mg once daily and zinc sulfate 220 mg capsule containing 50 mg elemental zinc twice daily for five days ($n = 411$)	HCQ 400 mg load followed by 200 mg twice daily for five days and azithromycin 500 mg once daily ($n = 521$)	Length of hospital stay; mechanical ventilation; oxygen flow rate; FiO2; ICU admission; length of ICU stay; death/hospice; intubation; discharge destination	In the unadjusted analysis, no outcomes were associated with zinc use. In bivariate logistic regression analysis, the addition of zinc sulfate was associated with decreased mortality or transition to hospice (OR 0.511, 95% CI 0.359–0.726), need for ICU (OR 0.545, 95% CI 0.362–0.821) and need for invasive ventilation (OR 0.562, 95% CI 0.354–0.891)	Serious risk of bias (ROBINS-I)
Chen et al. [35]	ChiCTR2000029559	China	Single-centre randomized controlled trial	Hospitalized not severe or critical patients with confirmed COVID-19 ($n = 62$)	HCQ 200 mg twice daily for 5 days ($n = 31$)	Standard care ($n = 31$)	Adverse events and time to clinical recovery	Compared with the control group, the body temperature and cough remission recovery times were significantly shortened in the HCQ treatment group. Two patients had mild adverse reactions in the HCQ treatment group.	Some concerns (Rob2)
Ip et al. [42]	NA	USA	Multicentre retrospective observational study	Hospitalized patients with COVID-19 ($n = 2512$)	Hydroxychloroquine, or hydroxychloroquine with azithromycin, or azithromycin alone ($n = 1914$)	No HCQ or AZ ($n = 598$)	In-hospital mortality; adverse events	No significant association between survival and any use of HCQ during the hospitalization (HR, 0.99 [95% CI, 0.80–1.22]), HCQ alone (HR, 1.02 [95% CI, 0.83–1.27]), or HCQ in combination with azithromycin (HR, 0.98 [95% CI, 0.75–1.28]).	Moderate risk of bias (ROBINS-I)
Kim et al. [37]	NA	Republic of Korea	Single-centre retrospective observational study	Hospitalized patients with COVID-19 ($n = 270$)	HCQ 200 mg tablets twice daily with or without antibiotics ($n = 22$)	Lopinavir 200 mg/ritonavir 50 mg tablets twice daily with or without antibiotics or standard of care ($n = 248$)	Time to complete or probable viral clearance; time to discharge; time to symptom resolution; adverse events	Time to viral clearance was significantly shorter with HQ plus antibiotics compared to Lopinavir/Ritonavir plus antibiotics (HR 0.49; 95% CI, 0.28–0.87) or conservative treatments (HR, 0.44; 95% CI, 0.25–0.78). Hospital length of stay was also shortest for patients treated with HQ plus antibiotics compared to other treatment groups. Both HQ and Lopinavir/Ritonavir showed side effects, none serious.	Serious risk of bias (ROBINS-I tool)
Magagnoli et al. [38]	NA	USA	Multicentre retrospective	Male hospitalized	HCQ or with azithromycin ($n = 210$)	No HCQ regimens ($n = 158$)	Discharge or death; need for mechanical	Death occurred in the 27.8% of the HC group vs 22.1% of the HC	Serious risk of bias

			observational study	patients with confirmed SARS-CoV-2 infection ($n = 368$)			ventilation	+ AZ group, and 11.4% of no HC group. Mechanical ventilation in the 13.3% of the HC group, 6.9% of the HC + AZ group, and 14.1% of the no HC group. Risk of death from any cause was higher in the HC group (aHR, 2.61; 95% CI, 1.10 to 6.17; $P = .03$). No significant differences in the risk of ventilation among the groups.	(ROBINS-I tool)
Mallat et al. [39]	NA	UAE	Single-centre retrospective observational study	Hospitalized patients with confirmed COVID-19 ($n = 34$)	HCQ 400 mg twice daily for 1 day, then 400 mg daily for 10 days ($n = 23$)	Non HCQ regimens ($n = 11$)	Time to SARS-CoV-2 negativity	The time to negativity was significantly longer in patients who received HCQ compared to those who did not receive the treatment (17 [13−21] vs. 10 [4–13] days, $p = .023$. This effect was confirmed in the adjusted analyses.	Serious risk of bias (ROBINS-I)
Ramireddy et al. [40]	NA	USA	Single-centre prospective observational study	Hospitalized patients with COVID-19 or under investigation ($n = 98$)	HCQ, azithromycin or their combination	No comparison	QTc prolongation	The 12% of the patients reached a critical level of QTc prolongation. Changes in QTc were highest with the combination treatment compared to either drug, especially vs. azithromycin alone (17 ± 39 vs. 0.5 ± 40 ms, $p = .07$). No patients manifested torsades de pointes.	Poor quality score (NOS)
Singh et al. [41]	NA	USA	Multicentre retrospective observational study	Hospitalized patients with COVID-19 ($n = 3372$)	HCQ treatment, with or without azithromycin ($n = 1125$)	Non HCQ treatment ($n = 2247$)	Mortality and need for mechanical ventilation at day 7 and day 14; adverse events	The estimated risk of mortality was similar in the treated vs control group at both day 7 (RR 1; 0.73–1.37) and day 14 (RR 1.04; 0.80–1.36). New ventricular arrythmias or cardiac arrest occurred in the 1.09% of the treated patients, with no significant differences compared to not treated.	Moderate risk of bias (ROBINS-I)

The table shows the main characteristics of the included studies, as reported by the authors.
Data are reported as percentages, mean ± standard deviation, median (interquartile range) or pointed estimates, as reported by the authors.
AZ: azithromycin; CI: confidence interval; COVID-19: coronavirus disease 2019; CQ: chloroquine; CT: computer tomography; ECG: electrocardiogram; HCQ: hydroxychloroquine; HR: Hazard Ratio; ICU: Intensive care unit; NA: Not available; PCR: Polymerase Chain Reaction; Rob2: Revised tool for Risk of Bias in randomized trials; ROBINS-I: Risk Of Bias in Non-randomized Studies of Interventions; NOS: Newcastle Ottawa Scale; USA: United States of America; UAE: United Arab Emirates.

[a] Under the column 'Outcomes' the main outcomes of the study and the evaluated safety outcomes are reported.

[b] Under the column 'Results' the most relevant findings are reported. For synthesis purpose, full results are not reported and can be retrieved from correspondent full-text papers.

[c] Under the column 'Risk of bias' the overall judgment about the risk of bias at individual study level is reported. Tools were used as appropriate and are also reported (Rob-2 [4]; ROBINS-I [5]; NOS [6]).

Rosenberg et al. conducted a retrospective multicentre study in 25 centres in New York, enrolling a random sample of 1475 patients among the 7914 patients hospitalized with a positive PCR test for SARS-CoV-2 [15] The cohort was subsequently divided to four groups: 1) HCQ alone (18.8%, $n = 271$); 2) HCQ + azithromycin (51.1%, $n = 735$); 3) azithromycin alone (15.4%, $n = 211$); 4) neither drug (15.4% $n = 221$). Analysis adjusted for patient demographics, preexisting conditions and illness severity as well as for treating hospital showed no significant association between treatment with HCQ + azithromycin (HR 1.35; 95% CI 0.76–2.40) or HCQ alone (HR 1.08; 95% CI 0.63–1.85) or azithromycin alone and higher risk of in-hospital death when compared to treatment with neither drug. Cardiac arrest and abnormal ECG findings (prolonged QT or arrhythmia) occurred more commonly among patients treated with HCQ + azithromycin (27.1% and 15.5% respectively) or HCQ alone (13.3% and 27.3%) than among those treated with azithromycin only (6.2% and 16.6%) or neither drug (6.8% and 14%). Adjusted analysis showed that patients receiving HCQ + azithromycin were at higher risk for cardiac arrest than those who received neither drug (OR 2.13; 95% CI 1.12–4.05) and those who received HCQ alone were at higher risk than those who received azithromycin alone (OR 2.97, 95% CI 1.56–5.64).

Tang et al. conducted a multicentre RCT in China wherein all eligible patients were intended to undergo stratified random sampling according to disease severity (mild/moderate or severe) to HCQ or standard care [16]. The primary study outcome was conversion of SARS–CoV–2 RT-PCR tests performed on specimens from the upper or lower respiratory tract to negative by day 28. Patients with severe organ failure (CNS, liver, renal) were excluded a-priori. Following enrollment of 150 hospitalized patients with confirmed (mostly mild) COVID-19 (treatment $n = 75$, controls $n = 75$) and conduction of a pre-planned interim analysis on day 13, the decline in new COVID-19 cases led to early study termination. The median time to conversion to a negative result was similar with HCQ (8; 95% CI 5–10 days) and with standard care (7; 95% CI 5–8 days) (HR 0.85, 95% CI 0.58–1.23; $P = .34$). Adverse events (mostly diarrhea but also dehydration, blurred vision and "disease progression") were recorded in 9% of the patients treated with standard care versus 30% of HCQ recipients.

Yu et al. conducted a single-centre retrospective study in China on 550 critically ill patients with confirmed COVID-19 [17]. The primary outcomes sought were mortality, hospital length of stay and the level of IL-6. The treatment group, comprised of 48 patients receiving 200 mg of hydroxychloroquine twice daily for 7–10 days, was compared to 502 patients in the control group receiving standard care. The use of HCQ was associated with a significantly decreased risk of death (adjusted HR: 0.36; 95% CI: 0.18–0.75; $P = .006$) and a longer duration of hospital stay before death [15 (IQR 10–21) versus 8 (IQR 4–14) days, $P < .05$].

3.3. Studies without a "no CQ/HCQ" comparison group

Borba et al. conducted a block-randomization phase IIb trial, enrolling hospitalized patients with severe acute respiratory syndrome (e.g. fever, tachypnea, hypotension, altered mental status, oliguria) and suspected diagnosis of COVID-19 in a single centre in Brazil [18]. Patients were enrolled before laboratory confirmation of COVID-19. The study aimed to compare the efficacy and safety of two doses of CQ base (600mgX2/day for 10 days vs. 450mgX2/day on day 0 and 450mgX1day on days 1–4). Placebo pills were used to mask the treatment from the participants and researchers. All patients also received azithromycin and some also received oseltamivir. The trial was terminated prematurely after enrolling 81 patients of the 440 intended when unplanned interim analysis was requested by the independent data and monitoring board due to concerns regarding safety. Higher drug doses were found to be accompanied by higher rates of 13-day mortality (39% vs. 15%), QTc interval prolongation >500 milliseconds (18.9% vs. 11.1%) and ventricular tachycardia (2 patients versus none). The proportion of patients with detectable viral RNA levels was similar in the two groups.

Million et al. conducted a nonrandomized single-arm study in one centre in France. The study included 1061 patients with a positive PCR test for SARS-CoV-2 who were admitted to either day-care or wards [19]. All patients received oral HCQ 200 mg X3/day for ten days and azithromycin 500 mg on the first day, followed by 250 mg daily for four days. All patients also underwent pre-treatment workup including electrocardiography and serum electrolyte testing to rule out the presence of contraindications to treatment. Good clinical outcomes, defined as survival, no ICU or hospital admission and negative nasal viral shedding were achieved in 91.7% of the patients by day 10. Adverse events occurred in 2.4% of the patients but none were cardiac. The same group of investigators published another article with similar methods and smaller sample size, without data overlap [20].

Molina et al. described a prospective case series of 11 patients. All the patients were treated with the same regimen proposed by the authors of the series of papers described above, but 80% of the patients had a positive PCR assay for nasopharyngeal swab specimens at 5–6 days [21].

3.4. Studies addressing cardiac adverse events

Mazzanti et al. prospectively studied 150 consecutive inpatients with positive PCR for SARS-CoV-2, treated with HCQ 400 mg (+ azithromycin 26%; + lopinavir-ritonavir 35%; both drugs 6%). An ECG was recorded after 5 days of treatment (QT corrected with Bazett formula). Proportion of patients with mild, moderate and severe (>500 ms) QT prolongation were 9%, 4% and 2% respectively. In 53% of cases who had an ECG off-therapy, the median increase of QTc was 18 ms [22].

Mercuro et al. retrospectively studied 90 patients hospitalized with laboratory confirmed COVID-19 who were given HCQ. Among these 53 concomitantly received azithromycin. The prolongation in QTc was greater in patients receiving combined HCQ and azithromycin treatment than in those receiving HCQ alone (HCQ ΔQTc of 5.5 ms, IQR −15.5–34.25 vs. 23 ms, IQR 10–40 for HCQ and AZ group; $p = .03$) [23]. The likelihood of QTc prolongation (>500 ms) was higher in patients taking loop diuretics, in those who had a baseline borderline QTc and in those fulfilling two or more SIRS criteria. Treatment with HCQ was interrupted due to QTc prolongation in 11% of the patients and one patient had Torsade de Pointes.

Chorin et al. retrospectively studied 251 hospitalized patients with COVID-19 receiving HCQ with azithromycin [24]. Only patients with a baseline and a follow-up ECG were included. These authors noted QTc prolongation (QTc > 60 ms) in 20% of the patients regardless of the initial QRS. One of the patients experienced Torsade de Pointes.

Maraj et al. retrospectively studied 91 patients admitted consecutively to a single centre for COVID-19 and treated with HCQ + azithromycin (dose not described) [25]. All patients underwent a baseline ECG and continuous telemetry monitoring. Almost one in four patients (23%) met the primary outcome which was development of significant QTc prolongation (Bazett formula), defined as an increase in baseline QTc ≥ 60 ms and/or absolute QTc > 500 ms. Although older age, concomitant cardiovascular and renal comorbidities and severe manifestation of COVID-19 were initially associated with QTc prolongation, in multivariable logistic regression analysis, only use of additional QT-prolonging drugs (mostly propofol) remained independently associated with the primary outcome (OR 3.69, 95% CI 1.22–11.2). One patient developed TdP and another developed polymorphic VT.

Bessiere et al. retrospectively studied 40 patients admitted to the ICU for COVID-19 and receiving either HCQ or azithromycin [26]. No patients had baseline risk factors for QTc prolongation. Ninety-three percent of patients had significant QTc prolongation and the treatments were suspended for this reason in 42.5%. The first two studies used a similar HCQ dose (400 mg twice at day 1 and then 400 mg daily/

200 mg twice daily) but only the second reported the dose of azithromycin (500 mg). In the last study, patients received HCQ 200 mg twice a day and 250 mg of azithromycin daily.

Van den Broek et al. retrospectively studied 95 patients, admitted with suspected COVID-19 in a single centre. Patients received chloroquine (600 mg loading dose followed by 300 mg twice daily) [27]. All patients had QTc prolongation (mean 34 ms, computer interpreted and adjusted with Bazett formula) and 23% had QTc prolongation >500 ms which led to dose modification/ treatment interruption. Saleh et al. conducted a prospective study including 201 consecutive patients hospitalized in three medical centers with confirmed COVID-19 PCR testing or high suspicion of COVID-19 with test pending, ARDS or severe illness characterized by SIRS criteria. The patients received CQ (5%, 500 mgX2 on day 0 then 500 daily on days 1–4) or HCQ (95%, 400mgX2 on day 0 then 200mgX2 on days 1–4) [28]. Fifty-nine percent of the patient cohort also received azithromycin. All electrocardiographic measurements were performed manually and Bazett formula was used to calculate the QTc. The maximum QTc during treatment was significantly higher in the group of patients treated with CQ/HCQ and azithromycin versus CQ/HCQ alone (453.3 ± 37.0 ms vs. 470.4 ± 45.0 ms, $p = .004$) but both groups had a similar change in the QTc from baseline to maximum QTc. Treatment was discontinued in seven patients (3.5%) due to QTc prolongation >500 ms. Seven patients had non-sustained monomorphic VT and one had sustained monomorphic VT. No episode of Torsade de Pointes was observed.

Peng et al. described the QTc in a case series of 13 patients with COVID-19 treated with HCQ (11 with azithromycin). QT prolongation was detected in 38.5% of the patients, normalizing after treatment completion or discontinuation. One nonagenarian died of sepsis [29].

3.5. Studies on prophylactic use

Boulware et al. conducted a randomized, double blind, placebo controlled trial in US and Canada, enrolling 821 asymptomatic non-hospitalized adults with self-reported high-risk or moderate risk of exposure to a positive COVID-19 case within 4 days of exposure. High risk was defined as household or occupational exposure at a distance of less than 6 ft. for more than 10 min while wearing neither a face mask nor an eye shield. Moderate risk was defined as exposure while wearing a face mask but no eye shield [30]. The study had a power of 90%; the sample size was calculated based on a prior study that had actively monitored exposed cases [31] where 10% of close contacts developed COVID-19 plus an attrition rate of 20%. Participants (recruited by social media) were assigned to HCQ (800 mg once, 600 mg 6–8 h later, then 600 mg daily for 4 days) or placebo and followed up through emails. Data were provided by participants via a portal to an online database. The median age of the cohort was 40 years, 66.4% were healthcare workers (HCWs) and the rate of adherence to the trial intervention was 79%. The incidence of new illness compatible with COVID-19 did not differ between those taking HCQ and those taking the placebo (11.8% vs. 14.3%; $p = .35$). Participant-reported side effects were more common in those receiving HCQ (40.1%) than placebo (16.8%). Gastrointestinal side effects were the most common and no serious adverse reactions were reported.

Nagaraya et al. performed a web-based survey among 166 HCWs in India, grouped into 'direct contact' (66.9%, involved in direct patient contact irrespective of personal protective equipment), 'indirect contact' (29.7% working in hospitals but no direct contact) and 'no contact' (3.4% working neither in hospital nor in a clinic). HCWs who had taken at least one dose of HCQ, were either negative to PCR SARS-CoV-2 test or not tested, had no symptoms compatible with the disease in the last 4 weeks and had not changed their usual medications recently were included. Thirty-eight percent of the surveyed HCWs reported at least one side effect, mostly gastrointestinal, neurological (e.g. headache), or not specific (e.g. fatigue). Prophylaxis with HCQ was initiated without performing an ECG in 80.1% of the cases. Six HCWs reported cardiovascular side effects, including palpitations ($n = 6$) and chest pain ($n = 2$) [32].

Gendelman et al. retrospectively analyzed prehospital data from 14,520 individuals screened for SARS-CoV-2 [33]. Among those screened 1317 tested positive. The infection rate among subjects who treated with HCQ for clinical indications other than treatment of COVID-19 was 0.23% compared to 0.25% in subjects who were not treated with HCQ ($P = .877$).

Konig et al. described a cohort of 80 patients with systemic lupus erythematosus and SARS-CoV-2 of which 51 patients (64%) were using CQ/HCQ. The proportion of patients hospitalized due to COVID-19 was similar among those using CQ/HCQ and among those who were not (55% [16/29]) vs. 57% [29/51], p = ns) [34].

3.6. Pre-print studies before peer review

Nine studies were retrieved from the search of pre-print repositories. These included one RCT [35] and eight nonrandomized studies [36-43]. The studies evaluated a total of 7702 hospitalized patients with COVID-19. We hereby describe only the RCT and the two retrospective studies that included the largest number of patients. A detailed description of all the studies is available in Table 1.

Chen et al. [35] conducted a single-centre controlled trial, randomizing 62 hospitalized severe or critical patients with COVID-19 to receive HCQ (200 mg twice daily for 5 days) or standard care. The authors registered significantly shortened body temperature recovery and cough remission times with HCQ. Two patients had mild adverse reactions in the HCQ treatment group.

Ip et al. retrospectively studied the files of 2512 COVID-19 patients with a positive PCR test hospitalized in 13 New Jersey hospitals (USA) [42]. HCQ was administered at the discretion of the treating teams with/without azithromycin or tocilizumab. Only 598 of the patients were not treated with HCQ and 1473 received hydroxychloroquine with azithromycin. Unadjusted data suggested higher mortality among patients receiving HCQ but adjusted with propensity modeling showed no differences in mortality with either HCQ alone (HR 1.02, 95% CI 0.83–1.27) or HCQ + azithromycin (HR 0.98, 95% CI 0.75–1.28). Discontinuation of HCQ due to QTc prolongation or arrhythmias was recorded in 4% and 2% of cases.

Singh et al. retrospectively identified 3372 patients hospitalized with COVID-19 in a multicentre database, of which 1125 were treated with HCQ. Cases were identified from diagnoses and laboratory findings based on WHO and CDC COVID-19 guidelines [41]. After propensity score matching, two cohorts of 910 patients (treated vs. not treated with HCQ) were compared. No significant differences were found in 7-day (RR 1; 0.73–1.37) or 14-day mortality (RR 1.04; 0.80–1.36) and in the rate of mechanical ventilation. New ventricular arrhythmias or cardiac arrest occurred in 1.09% of the treated patients, an incidence similar to that observed among those untreated (RR 0.63, 95%CI 0.28–1.37).

3.7. Risk of bias

Among the included studies, the six RCTs [11,13,16,18,30,35] were evaluated using the Rob2 tool [6]. Only two studies had low risk of bias [18,30]. Details regarding downgrading are provided in Fig. 1, and the weighted risk of bias is presented as a plot in Fig. S1 (Supplementary Material 4).

Fourteen [12,14,15,17,23,28,33,34,36-39,41,42] nonrandomized studies were evaluated using the ROBINS-I tool [7]. The most frequent domain causing downgrading was confounding. Details regarding downgrading are provided in Fig. 2**,** and the weighted risk of bias is presented as a plot in Fig. S2 (Supplementary Material 4). Twelve single-arm non randomized studies were assessed using the NOS [8] and all were rated as poor quality. The main cause of downgrading was lack

of comparability. Details regarding downgrading are provided in Supplementary Material 4 (Table S1).

3.8. Quantitative synthesis

We planned to perform quantitative synthesis if two or more studies were identified with a low risk of bias that also had sufficient homogeneity in study design, interventions and outcomes [10]. We identified only two studies with a low risk of bias, and these differed in participants (ill inpatients vs. exposed outpatients), intervention (treatment vs. prophylaxis) and outcomes (mortality rate vs. incidence of compatible illness with COVID-19) [18,30]. Therefore, particularly in light of the outcomes at stake, we decided to not perform quantitative synthesis of the data.

4. Discussion

Two months have elapsed since our previous systematic review on the topic of CQ/HCQ for the treatment of infection with SARS-CoV-2, in which we concluded that the literature on the topic does not suffice for recommendations but there is enough pre-clinical evidence to justify clinical trials [3]. In this time frame more than 6 million patients have been diagnosed. Media hysteria suggests that quite a few COVID-19 patients have been treated with CQ/HCQ. Our systematic review highlights the fact that, despite this, the quality of the existing literature remains poor on the topic and the data cannot be synthesized to clear conclusions regarding the efficacy and safety of these drugs. No high quality RCTs have been published to date evaluating the rates of either mortality or intubation. Although preliminary evidence suggests that treatment with CQ/HCQ may be associated with similar or even increased risk of death compared to standard care, these conclusions stem mostly from nonrandomized studies and the reasons of increased death remain not fully clarified.

The efficacy of a drug can only be assessed by comparing it to "standard care" or another drug. At this time only seven published trials (i.e. manuscripts that have undergone peer review) on the use of CQ/HCQ as a treatment have a comparator. Two of these trials included only 22 [13] and 30 [11] patients. A third included a large number of comparators

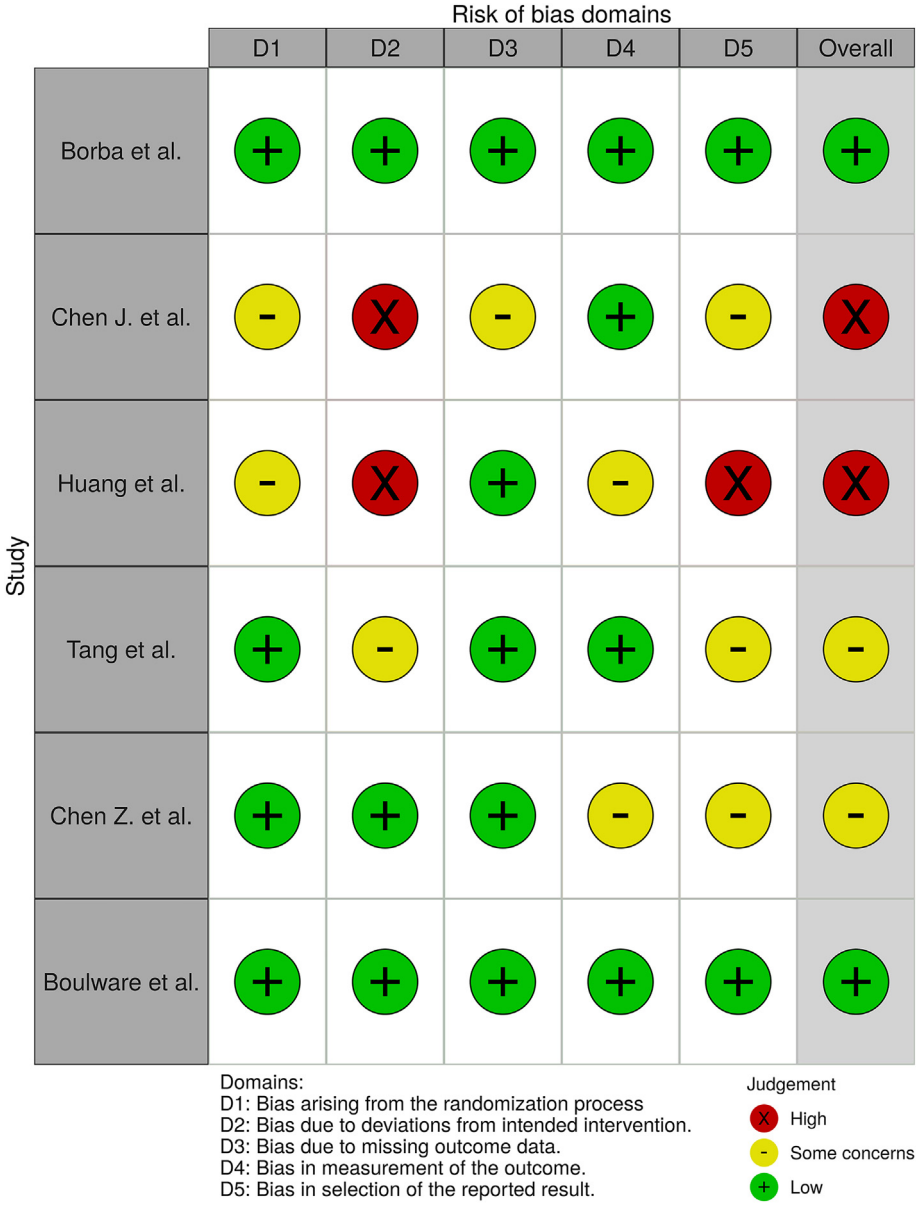

Fig. 1. Risk of bias of RCTs assessed using Rob2 tool.

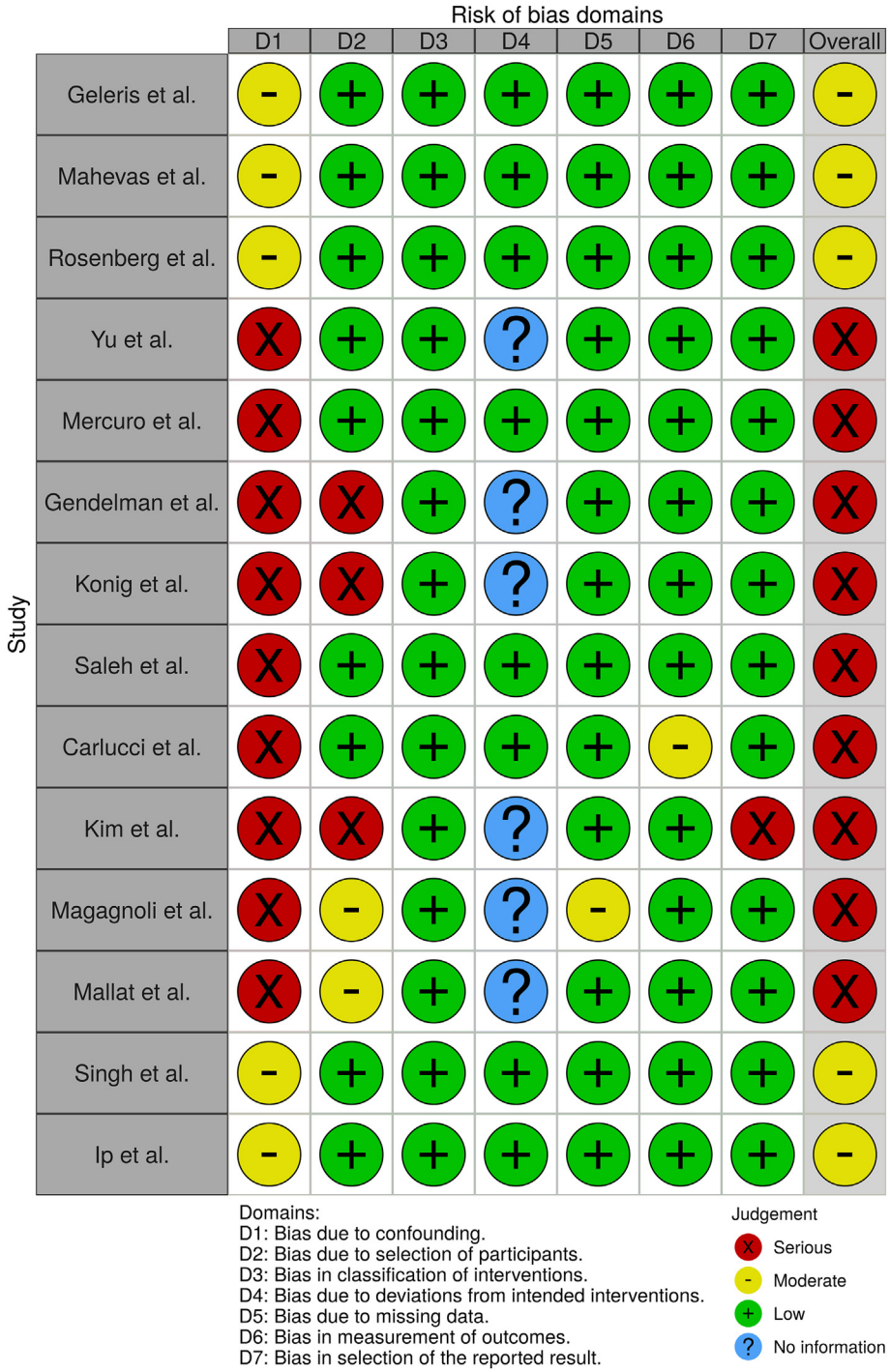

Fig. 2. Risk of bias of nonrandomized studies assessed using ROBINS-I tool.

but only 48 patients who actually received treatment [17] and in a fourth study only 75 patients were in the treatment arm [16]. The largest number of patients who actually received treatment in the published studies with comparators comes from one retrospective study (Rosenberg et al. $n = 1475$) [15] and one prospective study (Geleris et al. $n = 1376$) [12], both at moderate risk of bias. Both provided data from the same geographical area (New York). The first (multicentre) did not collect data on other antiviral drugs co-administered in included patients [15] and the second (single-centre) had a composite primary outcome measure [12]. Composite outcomes are often used to increase power, raising questions regarding outcome selection and interpretation [44]. The existing data regarding efficacy as treatment is also limited by issues that are not included in standard data quality tools. Two included RCTs were terminated early, one for concerns regarding side effects in a high CQ dose arm [18] and another due to a decline in cases [16]. These two studies were therefore underpowered for their primary outcomes. Underpowering has also been shown to be a major issue in studies on antiviral medications in patients with COVID-19 [45]. From the specific aspect of critical care, at least two of the studies included patients who were mostly not critically ill. One a-priori excluded patients with organ failure [16] and the second excluded patients who died within 24 h of presentation to hospital [12]. Finally,

Table 2
CQ and HCQ recommendations

	Treatment	Treatment dose	Recommendation
WHO (27th May 2020)	CQ or HCQ +/− Azithromycin	NA	Do not use as treatment or prophylaxis for COVID-19, outside of clinical trials. HCQ arm of solidarity trial resumed on 3rd June after a temporary stop
AIFA (29th May 2020)	HCQ alone or in combination with other drugs	Low doses are suggested, possibly for no more than 5–7 days	Do not use as treatment of prophylaxis outside of clinical trials
SIMIT (13th March 2020)	CQ or HCQ	CQ phosphate 500 mg BID for 10 days HCQ 200 mg BID	Do not use as prophylaxis
IDSA (11th April 2020)	CQ / HCQ alone or in combination with Azithromycin	NA	Use CQ/HCQ +/− Azithromycin only in the context of clinical trials among patients hospitalized for COVID/19
FDA (15th June 2020)	CQ or HCQ	NA	Use only in the context of clinical trials. FDA has revoked Emergency Use Authorization (EUA) on 15th June after the initial release in March 2020.
EMA (1st April 2020)	CQ or HCQ	NA	For patients: Only use chloroquine or hydroxychloroquine under medical prescription and supervision For healthcare providers: Use in clinical trials or in accordance with national established protocols CQ and HCQ should continue to be used in chronic conditions (e.g. rheumatological diseases)
SSC (28th March 2020)	CQ or HCQ	NA	There is insufficient evidence to issue a recommendation on the use of chloroquine or hydroxychloroquine as a treatment in critically ill adults with COVID-19
National Health Commission & National Administration of Traditional Chinese Medicine (7th version)	CQ phosphate	Adults aged 18–65 with bodyweight over 50 kg: CQ phosphate 500 mg bid for 7 days; Adults with body weight below 50 kg: 500 mg bid for Days1& 2 and 500 mg SID for Days 3–7	Possible use in hospital setting with attention to contraindication and adverse reactions

The table summarizes the leading recommendations for the use of CQ and HCQ as treatment or prophylaxis for COVID-19.
AIFA: Agenzia Italiana del Farmaco; BID: bis in die, twice a day; EMA: European Medicines Agency; FDA: Food and Drug Administration; IDSA: Infectious Disease Society of America; NA: not available; SID: semel in die, once a day; SIMIT: Società Italiana Malattie Infettive e Tropicali; SSC: Surviving Sepsis Campaign; WHO: World Health Organization.

all of the published studies reported all-cause mortality at various timepoints, rather than attributable mortality and none reported on the rate of withholding and withdrawal of care. This issue is particularly poignant since one of the studies reported that among the patients included almost half died without intubation [12]. The possibility of crisis standards of care is very valid in the context of a pandemic, and patients that do worse may have been more likely to receive both compassionate medication and expectant care.

Prolongation of QTc is a consistent finding with CQ/HCQ, suggesting that patients receiving treatment with CQ/HCQ require in the least periodic electrocardiographic assessment or, better yet, continuous monitoring. Higher doses of these drugs may be associated with higher risk of harm and side effects; however, this remains uncertain given that the study suggesting so was terminated very early [18]. Importantly, the association between CQ/HCQ and QT prolongation and arrhythmia was not adjusted for the presence of conventional risk factors for QT prolongation such as older age, electrolyte disorders, cardiac disease, genetic predisposition and other QT prolonging drugs in any of the studies.

Drug induced prolongation of the QT interval is a known risk factor for Torsades de Pointes but the exact electrographic markers of a tendency towards this arrhythmia remain unknown. Treatment with azithromycin has been associated with induction of short-coupled polymorphic VT irrespective of QT prolongation [46]. Conversely "the effect (of CQ/HCQ) on the QTc (is) driven entirely by prolonging the repolarization and regardless of QRS, as evident by the corresponding JTc prolongation" [24].

Reports of QTc prolongation and arrythmias during combination treatment of CQ/HCQ with azithromycin have been anecdotal thus far and mostly based on case reports [47]. The initial recommendation to combine the two drugs was based on the outcome of six patients [48] and has not been supported by any real evidence of benefit. One included nonrandomized large study suggest an independent association between the combination HCQ with azithromycin and higher risk of cardiac arrest compared to no drug (OR, 2.13, 95% CI 1.12–4.05) [15] and so it is probably time to rethink the efficacy and safety of this approach. More detailed study of the coupling interval of the arrhythmia-initiating beat may perhaps contribute to differentiate between ventricular arrythmias caused by the two drugs. Evidence from available data suggests that monitoring baseline and subsequent (e.g. daily) ECG during treatment especially in high risk patients with known risk.

We identified only two studies with low risk of bias (one for treatment and one for post-exposure prophylaxis) and our included studies varied widely in term of patients' characteristics, outcomes definitions, interventions and design (Table 1). Our early decision to proceed with quantitative synthesis only for the primary outcomes and only if the data would clearly lend itself to such analysis may seem conservative. However, given the stakes at hand such an approach may save lives as it should lead to better monitoring and research and, hopefully in the interim, individualized patient care.

While awaiting the results of large high-quality RCTs on CQ/HCQ treatment, the current level of evidence regarding the efficacy of and risk of this treatment, especially in specific patients, must be considered. Soon after the publication of the retracted article by Mehra et al. [49], data about safety were reviewed by the Data Safety Monitoring Board of the World Health Organization (WHO). The WHO has now decided to restart the HCQ arm of its Solidarity Trial notwithstanding [50]. Conversely, the principal investigators of the RECOVERY trial have recently released a statement reporting that, pending full results, recruitment to the HCQ treatment arm will be discontinued as preliminary results suggest no beneficial effect in patients hospitalized with COVID-19 [51]. Many national and international guidelines on COVID-19 have warned both patients and clinicians against the potential risk associated with

the use of CQ and HCQ (alone or in combination with azithromycin) and recommend the use of HCQ – azithromycin only in the context of clinical trials (Table 2).

Finally, we identified only one trial on post-exposure prophylaxis with HCQ. Although this trial seems appropriately powered and has a low risk of bias, delayed initiation of treatment (usually ≥3 days) and the use of self-reported outcomes make it of limited value. Therefore, at this time we have identified no evidence to either support or not support prophylaxis with HCQ.

The results of at least two more trials are anticipated with regards to treatment in patients with COVID-19 (NCT04315948; NCT04322123) and several trials are currently underway on prophylaxis with HCQ in people at high risk of SARS-CoV-2 infection (NCT04333732; NCT04303507; NCT04334148). The current state of affairs shows that this is the best way forward - quality data is likely to be generated only if treatment and prophylaxis of COVID-19 with CQ/HCQ are authorized within the context of clinical trials.

5. Conclusions

We found 32 studies for a total 29,192 studied participants but only two studies at low risk of bias, one on treatment and one on prophylaxis of COVID-19. Available evidence from moderate risk of bias studies suggests that treatment with CQ/HCQ confers no benefit in terms of mortality in hospitalized patients with COVID-19 compared to standard care. Furthermore, higher dose regimens and combination therapy with macrolide may be associated with harm. Postexposure prophylaxis with CQ/HCQ may not reduce the rate of COVID-19 but the quality of the evidence on this is low.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2020.06.019.

Authors' contribution

AC conceived the content, retrieved the data, wrote the manuscript and approved the final version. MI retrieved the data, wrote the manuscript and approved the final version. GI retrieved the data, wrote the manuscript and approved the final version. PI helped in data extraction and manuscript writing, revised the manuscript critically and approved the final version. AG conceived the content, helped in data extraction, revised the manuscript critically and approved the final version. SE conceived the content, helped in data extraction, wrote the manuscript and approved the final version.

Declaration of Competing interests

AC, GI, MI, PI, AG, SE declare to have no competing interests.

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None.

References

[1] Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): A review. JAMA 2020. https://doi.org/10.1001/jama.2020.6019.
[2] Taccone FS, Gorham J, Vincent JL. Hydroxychloroquine in the management of critically ill patients with COVID-19: The need for an evidence base. Lancet Respir Med 2020. https://doi.org/10.1016/S2213-2600(20)30172-7.
[3] Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care 2020. https://doi.org/10.1016/j.jcrc.2020.03.005.
[4] Cortegiani A, Ippolito M, Ingoglia G, Einav S. Chloroquine for COVID-19: Rationale, facts, hopes. Crit Care 2020;24:210. https://doi.org/10.1186/s13054-020-02932-4.
[5] Reeves BC, Deeks JJ, Higgins JPT, Shea B, PWG Tugwell. Chapter 24: Including non-randomized studies on intervention effects. Cochrane Handb Syst Rev Interv Version 60 (Updated July 2019) Cochrane 2019. https://training.cochrane.org/handbook/current/chapter-24. (accessed June 9, 2020).
[6] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 2019;366. https://doi.org/10.1136/bmj.l4898.
[7] Sterne JA, Hernán MA, Reeves BC, Savović 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. https://doi.org/10.1136/bmj.i4919.
[8] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5. https://doi.org/10.1007/s10654-010-9491-z.
[9] McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods n.d. https://doi.org/10.1002/jrsm.1411.
[10] Cochrane. Chapter 12: Synthesizing and presenting findings using other methods | Cochrane Training. Cochrane Handb Syst Rev Interv Version 60 (Updated July 2019) Cochrane; 2019. http://www.training.cochrane.org/handbook. (accessed June 9, 2020).
[11] Chen J, Liu D, Liu L, Liu P, Xu Q, Xia L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). Med Sci 2020;49:1–10. https://doi.org/10.3785/j.issn.1008-9292.2020.03.03.
[12] Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 2020. https://doi.org/10.1056/nejmoa2012410.
[13] Huang M, Tang T, Pang P, Li M, Ma R, Lu J, et al. Treating COVID-19 with chloroquine. J Mol Cell Biol 2020;00:1–4. https://doi.org/10.1093/jmcb/mjaa014.
[14] Mahévas M, Tran V-T, Roumier M, Chabrol A, Paule R, Guillaud C, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. BMJ 2019;2020:m1844. https://doi.org/10.1136/bmj.m1844.
[15] Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of Treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA 2020;12203:1–10. https://doi.org/10.1001/jama.2020.8630.
[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. https://doi.org/10.1136/bmj.m1849.
[17] Yu B, Li C, Chen P, Zhou N, Wang L, Li J, et al. Low dose of hydroxychloroquine reduces fatality of critically ill patients with COVID-19. Sci China Life Sci 2020. https://doi.org/10.1007/s11427-020-1732-2.
[18] Borba MGS, Val FFA, 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. JAMA Netw Open 2020;3:e208857. https://doi.org/10.1001/jamanetworkopen.2020.8857.
[19] Million M, Lagier J-C, Gautret P, Colson P, Fournier P-E, Amrane S, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. Travel Med Infect Dis 2020;101738. https://doi.org/10.1016/j.tmaid.2020.101738.
[20] Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Sevestre J, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. Travel Med Infect Dis 2020;34:101663. https://doi.org/10.1016/j.tmaid.2020.101663.
[21] Molina JM, Delaugerre C, Le Goff J, Mela-Lima B, Ponscarme D, Goldwirt L, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Mal Infect 2020;50:384. https://doi.org/10.1016/j.medmal.2020.03.006.
[22] Mazzanti A, Briani M, Kukavica D, Bulian F, Marelli S, Trancuccio A, et al. Association of hydroxychloroquine with QTc interval in patients with COVID-19. Circulation 2020. https://doi.org/10.1161/CIRCULATIONAHA.120.048476.
[23] Mercuro NJ, Yen CF, Shim DJ, Maher TR, McCoy CM, Zimetbaum PJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for Coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020:1–6. https://doi.org/10.1001/jamacardio.2020.1834.
[24] Chorin E, Wadhwani L, Magnani S, Dai M, Shulman E, Nadeau-Routhier C, et al. QT interval prolongation and Torsade De Pointes in patients with COVID-19 treated with hydroxychloroquine/azithromycin. Heart Rhythm 2020. https://doi.org/10.1016/j.hrthm.2020.05.014.
[25] Maraj I, Hummel JP, Taoutel R, Chamoun R, Workman V, Li C, et al. Incidence and determinants of QT interval prolongation in COVID-19 patients treated with hydroxychloroquine and azithromycin. J Cardiovasc Electrophysiol 2020. https://doi.org/10.1111/jce.14594.
[26] Bessière F, Roccia H, Delinière A, Charrière R, Chevalier P, Argaud L, et al. Assessment of QT intervals in a case series of patients with Coronavirus disease 2019 (COVID-19) infection treated with hydroxychloroquine alone or in combination with azithromycin in an intensive care unit. JAMA Cardiol 2020:3–5. https://doi.org/10.1001/jamacardio.2020.1787.
[27] van den Broek MPH, Möhlmann JE, Abeln BGS, Liebregts M, van Dijk VF, van de Garde EMW. Chloroquine-induced QTc prolongation in COVID-19 patients. Netherlands Heart J 2020:1–4. https://doi.org/10.1007/s12471-020-01429-7.

[28] Saleh M, Gabriels J, Chang D, Kim BS, Mansoor A, Mahmood E, et al. The effect of chloroquine, hydroxychloroquine and azithromycin on the corrected QT interval in patients with SARS-CoV-2 infection. Circ Arrhythmia Electrophysiol 2020. https://doi.org/10.1161/CIRCEP.120.008662.

[29] Peng HC, Hussin N, Nalliah S, Ooi WT, Tang XY, Zachariah S, et al. Experience of short-term hydroxychloroquine and azithromycin in COVID-19 patients and effect on QTc trend. J Infect 2020. https://doi.org/10.1016/j.jinf.2020.05.058.

[30] Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2016638.

[31] Burke RM, Midgley CM, Dratch A, Fenstersheib M, Haupt T, Holshue M, et al. Active monitoring of persons exposed to patients with confirmed COVID-19 - United States, January–February 2020. MMWR Morb Mortal Wkly Rep 2020;69:245–6. https://doi.org/10.15585/mmwr.mm6909e1.

[32] Nagaraja BS, Ramesh KN, Dhar D, Mondal MS, Dey T, Saha S, et al. HyPE study: Hydroxychloroquine prophylaxis-related adverse events' analysis among healthcare workers during COVID-19 pandemic: a rising public health concern. J Public Health (Bangkok) 2020. https://doi.org/10.1093/pubmed/fdaa074.

[33] Gendelman O, Amital H, Bragazzi NL, Watad A, Chodick G. Continuous hydroxychloroquine or colchicine therapy does not prevent infection with SARS-CoV-2: Insights from a large healthcare database analysis. Autoimmun Rev 2020. https://doi.org/10.1016/j.autrev.2020.102566.

[34] Konig M, Kim AH, Scheetz MH, Graef ER, Liew JW, Simard J, et al. Baseline use of hydroxychloroquine in systemic lupus erythematosus does not preclude SARS-CoV-2 infection and severe COVID-19. Clin Transl Sci 2020. https://doi.org/10.1111/cts.12797.

[35] 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. https://doi.org/10.1101/2020.03.22.20040758.

[36] Carlucci P, Ahuja T, Petrilli C, Rajagopalan H, Jones S, Rahimian J. Hydroxychloroquine and azithromycin plus zinc vs hydroxychloroquine and azithromycin alone: outcomes in hospitalized COVID-19 patients. MedRxiv 2020. https://doi.org/10.1101/2020.05.02.20080036.

[37] Seo Kim M, Jang S-W, Park Y-K, Kim B-O, Hwang T-H, Ho Kang S, et al. Treatment response to hydroxychloroquine, lopinavir-ritonavir, and antibiotics for moderate COVID-19: A first report on the pharmacological outcomes from South Korea. MedRxiv 2020. https://doi.org/10.1101/2020.05.13.20094193.

[38] Magagnoli J, Narendran S, Pereira F, Cummings T, Hardin JW, Sutton SS, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. MedRxiv 2020. https://doi.org/10.1101/2020.04.16.20065920.

[39] Mallat J, Hamed F, Balkis M, Mohamed M, 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. https://doi.org/10.1101/2020.04.27.20082180.

[40] Ramireddy AHC, Reinier K, Ebinger J, Park E, Thompson M, et al. Experience with hydroxychloroquine and azithromycin in the COVID-19 pandemic: Implications for QT interval monitoring. MedRxiv n.d. https://doi.org/10.1101/2020.04.22.20075671.

[41] Singh S, Khan A, Chowdhry M, Chatterjee A, Shailendra A, Khan A, et al. Outcomes of hydroxychloroquine treatment among hospitalized COVID-19 patients in the United States- Real-world evidence from a healthcare network for design assistance to complete this project. MedRxiv 2020. https://doi.org/10.1101/2020.05.12.20099028.

[42] Ip A, Berry DA, Hansen E, Goy AH, Pecora AL, Sinclaire BA, et al. Hydroxychloroquine and tocilizumab therapy in COVID-19 patients - An observational study. MedRxiv 2020. https://doi.org/10.1101/2020.05.21.20109207.

[43] Ahmad I, Alam M, Saadi R, Mahmud S, Saadi E. Doxycycline and hydroxychloroquine as treatment for high-risk COVID-19 patients: Experience from case series of 54 patients in long-term care facilities. MedRxiv 2020. https://doi.org/10.1101/2020.05.18.20066902.

[44] Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials: greater precision but with greater uncertainty? JAMA 2003;289:2554–9. https://doi.org/10.1001/jama.289.19.2554.

[45] Norrie JD. Remdesivir for COVID-19: challenges of underpowered studies. Lancet 2020. https://doi.org/10.1016/S0140-6736(20)31023-0.

[46] Yang Z, Prinsen JK, Bersell KR, Shen W, Yermalitskaya L, Sidorova T, et al. Azithromycin causes a novel proarrhythmic syndrome. Circ Arrhythmia Electrophysiol 2017;10. https://doi.org/10.1161/CIRCEP.115.003560.

[47] Hancox JC, Vieweg WVR, Hasnain M, Crouse ELB, Baranchuk A. Azithromycin, cardiovascular risks, QTc interval prolongation, torsade de pointes, and regulatory issues: A narrative review based on the study of case reports. Ther Adv Infect Dis 2013;1:155–65. https://doi.org/10.1177/2049936113501816.

[48] Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;105949. https://doi.org/10.1016/j.ijantimicag.2020.105949.

[49] Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: A multinational registry analysis. Lancet 2020;6736:1–10. https://doi.org/10.1016/S0140-6736(20)31180-6.

[50] WHO. WHO Director-General's opening remarks at the media briefing on COVID-19 - 3 June 2020. n.d. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—03-june-2020.

[51] Chief Investigators of the Randomised Evaluation of COVid-19 thERapY. No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19 — RECOVERY Trial n.d. https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19 (accessed June 8, 2020).