Hydroxychloroquine and chloroquine for treatment of coronavirus disease 19 (COVID-19): a systematic review and meta-analysis of randomized and non-randomized controlled trials

Risa Ebina-Shibuya[1], Ho Namkoong[2], Nobuyuki Horita[3], Hideaki Kato[4], Yu Hara[3], Nobuaki Kobayashi[3], Takeshi Kaneko[3]

[1]Laboratory of Molecular Immunology, Immunology Center, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA; [2]Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA; [3]Department of Pulmonology, Yokohama City University Graduate School of Medicine, Yokohama, Japan; [4]Infection Prevention and Control Department, Yokohama City University Hospital, Yokohama, Japan

Contributions: (I) Conception and design: R Ebina-Shibuya, Y Hara, N Kobayashi; (II) Administrative support: T Kaneko; (III) Provision of study materials or patients: R Ebina-Shibuya, H Namkoong, N Horita; (IV) Collection and assembly of data: R Ebina-Shibuya, H Namkoong, N Horita; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Nobuyuki Horita, MD, PhD. Department of Pulmonology, Yokohama City University Graduate School of Medicine, 3-9, Fukuura, Kanazawa, Yokohama, Japan. Email: horitano@yokohama-cu.ac.jp.

Background: Although the US government approved hydroxychloroquine (HCQ) and chloroquine (CQ) for hospitalized coronavirus disease 19 (COVID-19) patients, some studies denied efficacy of HCQ and CQ. We aimed to evaluate HCQ/CQ treatment for COVID-19.

Methods: Five databases were searched on April 15, 2020, without publication date restriction. We followed both Preferred Reporting Items for Systematic Reviews and Meta-analyses and Meta-analysis of Observational Studies in Epidemiology statement reporting recommendations. A random-model meta-analysis was conducted to pool odds ratio (OR) and hazard ratio (HR). The quality of evidence for each outcome and the final recommendation was assessed using the GRADE guidelines of the American College of Chest Physicians.

Results: We identified four randomized controlled trials (RCTs) and four observational studies with 2,063 COVID-19 cases. All-cause mortality was not affected by the administration of HCQ/CQ [OR: 1.05, 95% confidence interval (CI): 0.53–2.09, P=0.89]. No improvement of viral clearance was found neither by time-to-event analysis (HR: 1.19, 95% CI: 0.74–1.94, P=0.47) nor frequency on day 7 (OR: 1.47, 95% CI: 0.33–6.63, P=0.62). HCQ/CQ treatment increased the risk of the any adverse event with OR of 3.56 (95% CI: 1.62–7.83, P=0.002).

Conclusions: HCQ/CQ failed to decrease the all-cause mortality (very low quality evidence) and did not improve viral clearance (low or very low quality evidence) but increased the risk of any adverse event (moderate quality evidence). Routine administration of HCQ/CQ for COVID-19 patients is not recommended (weak recommendation, Grade 2C).

Keywords: Virus diseases; aminoquinolines; evidence-based medicine; drug approval; policy making; coronavirus disease 19 (COVID-19)

Introduction

As of April 22, 2020, more than 2.5 million people have been diagnosed with coronavirus disease 2019 (COVID-19). It is caused by a novel coronavirus, severe acute respiratory syndrome coronavirus (SARS-CoV-2), which causes severe pneumonia leading to fatal respiratory failure (1). Several existing drugs including the antimalarials, chloroquine (CQ) and hydroxychloroquine (HCQ), have been extensively studied as possible treatment candidates. A Chinese expert panel recommended CQ for COVID-19 cases in February 2020, primarily based on *in vitro* data and clinical data from CQ-treated patients who were infected with other pathogens (2). *In vitro*, CQ potently blocked SARS-CoV-2 infection at low micromolar concentrations with a high selectivity index (3). In mid-March 2020, a small size non-randomized clinical trial conducted by Gautret *et al.* revealed that HCQ treated COVID-19 patients experienced more rapid viral load reduction than did those without HCQ (4). At the end of March 2020, the US Food and Drug Administration (FDA) authorized clinicians to prescribe HCQ/CQ for hospitalized patients without any evidence generated from a randomized controlled trial (RCT) (5,6).

Presently perception is that HCQ and CQ, which are safe, old, and cheap drugs with antiviral efficacy, have clinical applicability to SARS-CoV-2. Nonetheless, their efficacy remains unclear due to the lack of conclusive data from RCTs. Moreover, the narrow margin of safety of CQ occasionally causes severe side effects including central nervous disorders, ocular manifestations, and arrhythmia due to QT prolongation (7). Although HCQ is safer than CQ, uncontrolled use of these drugs can lead to serious toxicities. Another concern is the possible shortage of CQ and HCQ for well-established treatment indications, which would adversely affect people with rheumatological disorders, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and primary Sjögren syndrome (8). Several randomized and non-randomized controlled trials with conflicting results have been reported from China and France since mid-March (4,9-14). Based on the results of these studies, we performed a systematic review and meta-analysis to provide deeper insights about the suitability of HCQ/CQ for the treatment of COVID-19. We present the following article in accordance with the PRIMSA reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-2022).

Methods

Overview

Patient informed consent and institutional ethics review board approval were not applicable since our review did not directly deal with patients and clinical data. The protocol has been registered on the University hospital Medical Information Network Center Clinical Trial Registry (UMIN-CTR, Japan) as UMIN000040188 (15). Our systematic review followed Preferred Reporting Items for Systematic Reviews and Meta-analyses and Meta-analysis of Observational Studies in Epidemiology statement (16,17).

Study search

We searched for candidate articles using PubMed, Cochrane CENTRAL, EMBASE, and Web of Science Core Collection on April 15th, 2020. To detect non-peer reviewed recent articles, medRxiv was also searched. Search strategy is presented elsewhere (Appendix 1).

Publication type

RCTs and observational studies that compared treatment with and without HCQ/CQ written in any language were included. A retrospective study that compared treatment outcome by HCQ/CQ regimen and non-HCQ/CQ regimen was added. Our analysis did not exclude conference abstracts and non-peer reviewed articles. Single-arm studies and case reports were not included because these studies do not have control arms. For studies that included three or more arms, we extracted the HCQ/CQ arm and the most appropriate counterpart arm.

Patient

Only studies with confirmed COVID-19 diagnosis patient were included. Although we did not pre-specify diagnosis method and patient disposition, only hospitalized patients with PCR confirmed diagnoses were recruited in the studies that we finally evaluated.

Treatment

A patient in the HCQ/CQ arm should be treated with HCQ or CQ at any dosage for any duration. Concomitant administration of azithromycin (AZM) was permitted.

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Outcome

Protocol specified primary outcomes were all-cause mortality and viral clearance. Viral clearance was chosen as a primary outcome because enhanced viral clearance with HCQ has been reported from a French non-randomized trial, which contributed to US FDA approval of HCQ and CQ (4-6).

Secondary outcomes included time to discharge, symptom alleviation, CT image improvement, disease progression defined as a composite outcome with death and intensive care unit (ICU) admission, any adverse event, and serious adverse event.

For viral clearance and CT improvement, we extracted both time-to-event hazard ratio (HR) and event occurrence at day 7. In the absence of day 7 data, data on day 6 or 8 were used instead.

Subgroup analysis

Subgroup analyses for all outcomes from RCTs and observational studies were performed.

Study selection and data extraction

Articles found in PubMed, Embase, Web of Science, and Cochrane were screened based on title and abstract information, scrutinized through full-article reading performed independently by two review authors (RES & NH), who also extracted necessary data independently. Similarly, articles from medRxiv were processed by two review authors (HN & NH).

For observational studies, multiple variate-adjusted value or propensity score weighted value was used when available. Study characteristics such as study design, treatment regimen, and trial size and outcome such as mortality and viral clearance were extracted. We did not try to contact authors of the original studies because we aimed an expedited reporting.

Quality assessment

Because the widely used Cochrane Risk of Bias tool is designed for RCTs, we assessed the risk of bias of each study with the concept of Cochrane Risk of Bias tool and described the methodological weaknesses that may lead to high risk of bias (18).

Statistics

Dichotomous outcomes were compared using the Mantel-Haenszel odds ratio (OR). When one or more cells in the two-by-two contingency were null, 0.5 was added to all the cells. HRs were pooled after logarithmic transformation. The inverse variance method was used where appropriate. When data were obtainable, intention-to-treat analysis was preferred except for adverse event analysis, for which safety analysis sets should be used. Kaplan-Meier curves were read using Parmer's method as deemed necessary (19).

A random-effect model meta-analysis was performed using Review Manager version 5 (Cochrane, London, UK). Publication bias was not assessed due to the number of studies, which was less than 10.

Quality of evidence and recommendation

Quality of evidence of each outcome was judged as high, moderate, low, or very low as per the GRADE guideline (20) Final grade of recommendation was decided based on the system used by the American College of Chest Physicians (21).

Results

Study selection

We found 319 articles by electronic search and two additional articles from hand search. Of 321 articles that met the preliminary criteria, 53, 234, and 26 were excluded through removal of duplication, title/abstract screening, and full-article scrutinizing, respectively (*Figure 1*). Ultimately, we selected eight articles for our quantitative synthesis (4,9-14,22,23) (*Table 1*, *Figure 1*).

Characteristics of included studies

The eight research papers consisted of four RCT and four observational studies, five were from China, and two were from France, one was from USA; seven were written in English language, and one was written in Chinese language (*Table 1*). One article we found in medRxiv was published in peer reviewed article after the submission of our first draft (12,22). Numbers of patients included in each study ranged from 22 to 1,438 with a median of 130, a total of 2,063. Four adopted HCQ regimens, two used CQ regimens, one used an HCQ + AZM regimen, and one adopted a factorial
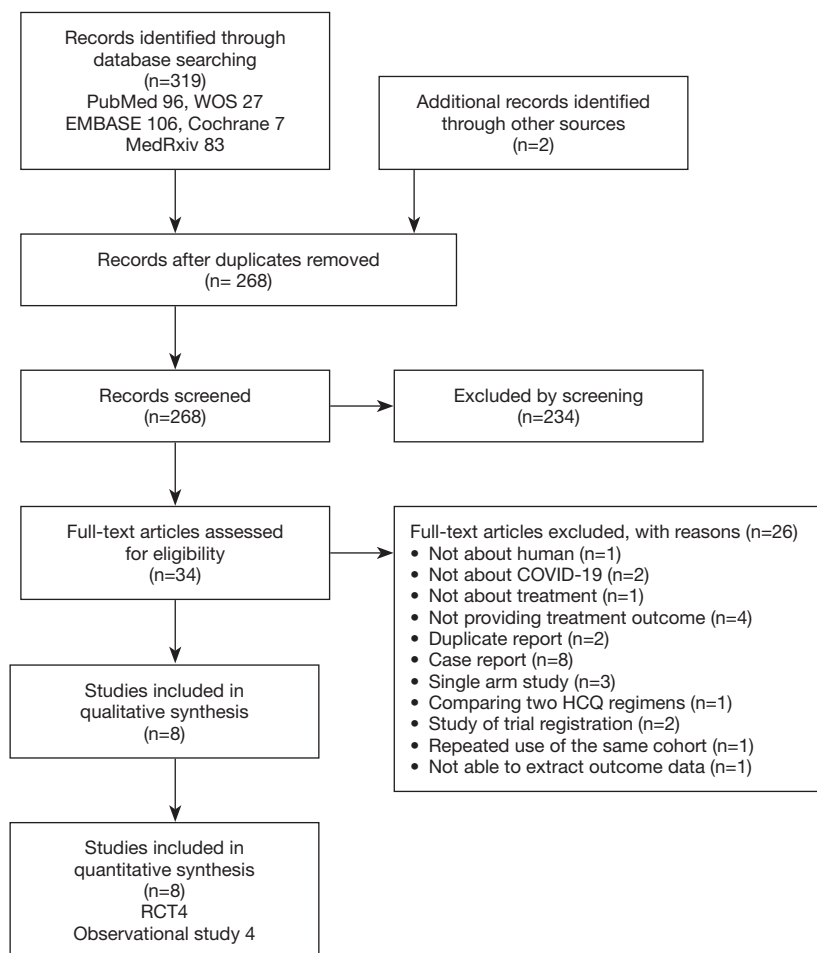
Figure 1 PRISMA flow diagram. WOS, Web of Science; HCQ, hydroxychloroquine; COVID-19, coronavirus disease 19.

design combining HCQ and AZM. Doses of HCQ ranged from 400 to 1,200 mg/day. Two retrospective observational study did not specify the HCQ/CQ dosage. One study administered Lopinavir/Ritonavir as a counterpart of HCQ/CQ, while the other seven did not employ any specific anti-viral treatment. According to five reports that described disease severity, most patients had asymptomatic, mild, or moderate disease with three exceptions: Tang *et al.* and Huang *et al.* randomized two and eight severe cases (11,12,22), respectively; and approximately 16% of COVID-19 cases reported by of Chen *et al.* were serious or critical (*Table 1*). Each study had several methodological weaknesses which led to high risks of bias as shown in *Table 1*.

All-cause mortality

A study by Rosenberg recorded by far the largest number

of death cases. This observational study compared four arms, HCQ + AZM, HCQ alone, AZM alone, and neither of them. Therefore, we derived two comparison from this study: "HCQ + AZM versus AZM alone" and "HCQ alone versus neither of them". All-cause mortality was not affected by the administration of HCQ/CQ [OR: 1.05, 95% confidence interval (CI): 0.53–2.09, P=0.89; I²=31%, P for heterogeneity 0.18; *Figure 2A*].

Viral clearance

According to time to event analysis, HCQ/CQ treatment did not facilitate the viral clearance (HR: 1.19, 95% CI: 0.74–1.94, P=0.47; I²=57%, P for heterogeneity 0.07; *Figure 2B*).

Data for viral clearance at day 7 were reported in four articles. Sixty-nine (55%) out of 126 HCQ/CQ treated patients and 67 (57%) out of 118 patients in the control arm

Table 1 Characteristics of included studies

Author	Country	Language	Design	Diagnosis	N(H)CQ/Ctl	HCQ/CQ regimen	Counterpart regimen	Age	M/F	Severity	Baseline imbalance	Methodological weakness led to high risk of bias
Randomized controlled trials												
Chen J	China	Chinese	Open RCT	PCR	15/15	HCQ 400 mg qd, d1–5	None	48.6	21/9	Unclear	None	Not blinded
Chen Z	China	English	RCT	rtPCR	31/31	HCQ 200 mg bid, d1–5	None	44.7	29/33	Mild, pneumonia	None	No description of blinding
Huang	China	English	RCT	rtPCR	10/12	CQ 500 mg bid, d1–10	Lopinavir/ ritonavir 400/100 mg bid d1–10	44	13/9	Moderate 14, severe 8	Earlier treatment in CQ arm (2.5 vs. 6.5 d, P<0.001)	No description of blinding; not registered; baseline imbalance
Tang	China	English	Open RCT	Real time rtPCR	75/75	HCQ 1,200 mg d1–3; 800 mg d4–21	None	46.1	82/68	Mild/ moderate 148, severe 2	None	Not blinded
Observational studies												
Chen X	China	English	Retro obs	Real time rtPCR	17/121	CQ dose unspecified	None	Apx 48	Apx 54%/46%	Moderate or less: apx 84%, serious/ critical: apx 16%	Unclear	Not registered retrospective design; inconsistent CQ dosage; not adjusted for covariate; lack of basal data in each arm
Gautret	France	English	Pro obs	Real time rtPCR	26/16	HCQ 200 mg tid (+AZM 500 mg d1, 250 mg d2–; 6 patient)	None	Apx 45.1	Apx 42%/58%	Unclear	Elder in HCQ arm (mean 51 vs. 37 yo, P=0.06)	Attenuation in HCQ arm; less recruited than protocol; inconsistent addition of azm; baseline imbalance; not adjusted for covariate
Rosenberg	USA	English	Retro obs	Laboratory confirmed	735/271/ 211/221	HCQ + AZM/HCQ/ AZM/neither, dose unspecified	Four-arm factorial design	Apx 60	858/580	Unclear	HCQ + AZM and HCQ were more frequently used for shock and oxygen desaturation cases	Not registered retrospective design; inconsistent CQ dosage; baseline imbalance
Mahevas	France	English	Retro obs, propensity score	PCR	84/97	HCQ 600 mg/d	None	60	128/33	Moderate (O$_2$, not ICU), Pneumonia	None	Not registered retrospective design

Age: median or mean age. Apx: approximately, exact data were unclear because Chen et al. aggregated data including cases who were treated with other antiviral drugs and because Gautret et al. presented data after excluding lost cases. RCT, randomized controlled trial; pro obs, prospective observational study; retro obs, retrospective observational study; rtPCR, reverse transcription PCR; N(H)CQ/Ctl, numbers of patients in HCQ/CQ arm and control arm; CQ, chloroquine; HCQ, hydroxychloroquine; AZM, azithromycin; M/F, male female ratio.
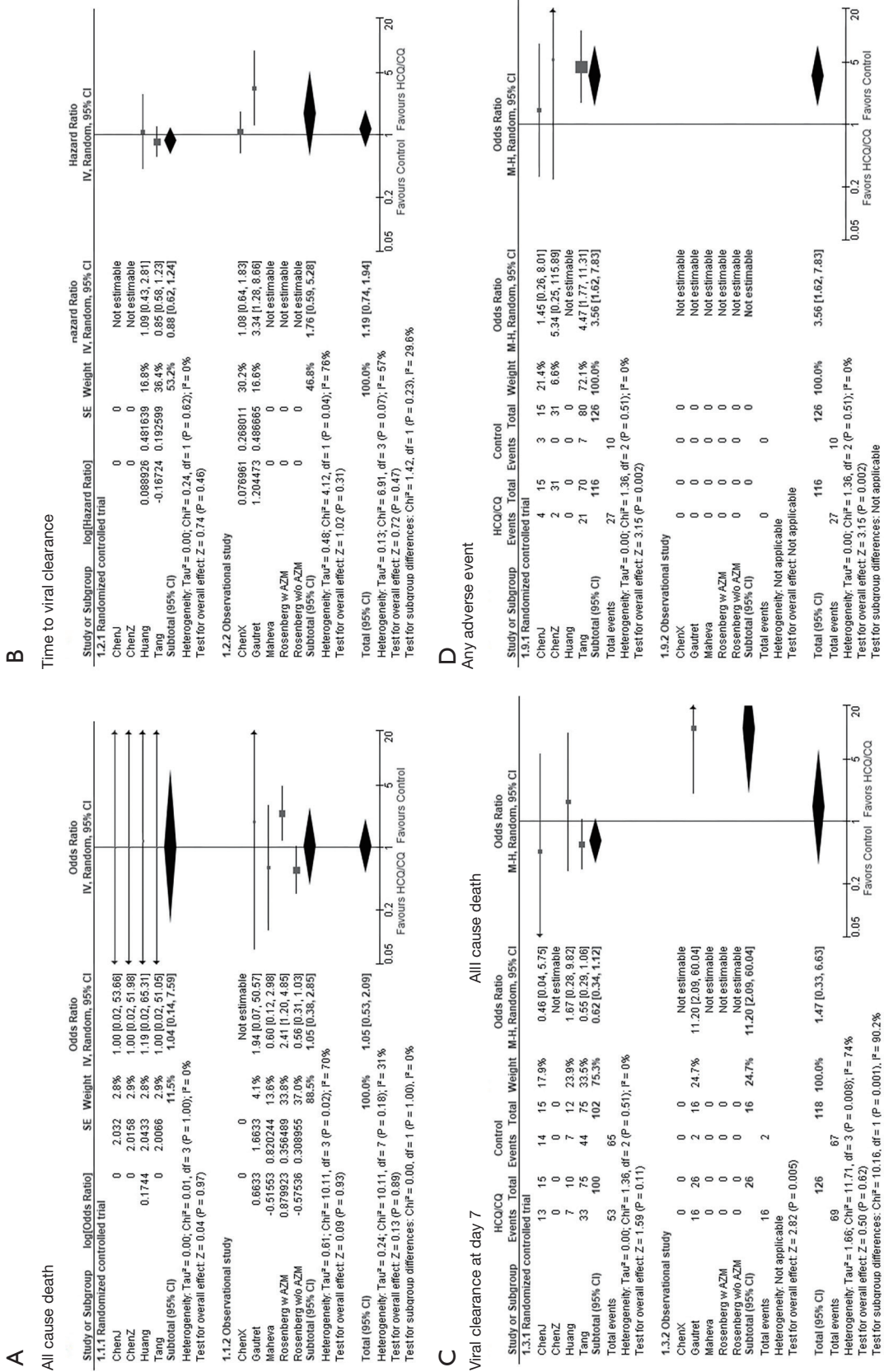
Figure 2 Forest plots for selected outcomes. (A) All cause death; (B) time to viral clearance; (C) viral clearance at day 7; (D) any adverse event. Rosenberg w AZM (with AZM): "HCQ + AZM versus AZM alone". Rosenberg w/o AZM (without AZM): "HCQ alone versus neither of them". SE, standard error; 95% CI, 95% confidence interval; IV, inverse variance; M-H, Mantel-Haenszel; HCQ/CQ, hydroxychloroquine/chloroquine; AZM, azithromycin.

achieved viral clearance at day 7. There was no difference in the frequency of day 7 viral clearance between the arms (OR: 1.47, 95% CI: 0.33–6.63, P=0.62; *Figure 2C*). Substantial overall heterogeneity (I^2=74%, P for heterogeneity <0.001) may be attributed to the study design (I^2=90.2%, P for subgroup difference <0.001).

Time to discharge

A random-model meta-analysis with two studies consisted of 160 patients showed that HCQ/CQ resulted in a tendency toward faster discharge with an HR of 2.29 (95% CI: 0.72–7.27, P=0.16; I^2=73%, P for heterogeneity 0.06; Figure S1).

Time to symptom alleviation

An RCT by Tang *et al.* is the only trial that provided a HR for time to symptom alleviation. However, this trial found no difference for symptom alleviation (HR: 1.01, 95% CI: 0.59–1.75, P=0.97; Figure S2)

Time to CT image improvement

Huang *et al.* reported a small size RCT with 22 patients, which compared CQ 500 mg po twice daily for 10 days and oral Lopinavir and Ritonavir. CQ regimen was associated with a tendency toward faster CT image improvement (HR: 2.42, 95% CI: 0.83–7.05, P=0.10; Figure S3).

HCQ/CQ administration was not associated with frequency of CT image improvement at day 7 (OR: 1.22, 95% CI: 0.28–5.29, P=0.79; I^2=54%, P for heterogeneity 0.11; Figure S4)

Disease progression

Two observational studies provided data on the composited outcome of death and ICU admission. The pooled OR from these two studies with 223 patients was 1.41 (95% CI: 0.28–7.05, P=0.68; I^2=37%, P for heterogeneity 0.21; Figure S5)

Adverse event

Random-model meta-analyses of three RCTs consisting of 242 cases indicated that HCQ/CQ treatment increased the risk of any adverse event with OR of 3.56 (95% CI: 1.62–7.83, P=0.002) and without heterogeneity (I^2=0, P for heterogeneity 0.51; *Figure 1D*). However, administration

of HCQ/CQ did not lead to a significant increase of severe adverse event (OR: 2.11, 95% CI: 0.27–16.68, P=0.48; I^2=0%, P for heterogeneity 0.74; Figure S6).

Quality of evidence and recommendation

The findings from the current systematic review and meta-analysis accompanied with graded evidence level of each outcome are summarized in *Table 2* (20).

Therefore, with this body of evidence, it is not recommended to administrate HCQ/CQ for COVID-19 cases (weak recommendation, low or very low quality evidence, Grade 2C) (21).

Sensitivity analysis focusing peer reviewed articles

Although this analysis was not specified in the protocol, some may want to know excluding non-peer reviewed articles may alter the primary endpoint results. Analysis based on peer reviewed article only did not change the conclusion as shown in Figure S7.

Discussion

We have performed a systematic review and meta-analysis, quantitatively integrating four RCTs and four observational studies involving 2,063 patients, to elucidate how HCQ/CQ affects COVID-19 clinical outcomes. The first peer-reviewed clinical study that evaluated efficacy of HCQ with a non-HCQ arm was reported by Gautret *et al.* from France (4) on March 20, 2020. At day 6 post-inclusion, 70% of HCQ-treated patients achieved viral clearance compared to 12.5% in the control group (P=0.001) (4). This drastic therapeutic impact of HCQ facilitated US FDA approval of HQC and QC to treat SARS-CoV-2 infection (5,6). However, three subsequent RCTs did not reproduce this (9,11,12). Our analysis did not confirm any clinical benefit including SARS-CoV-2 clearance by HCQ/CQ administration this treatment increased any adverse events (OR: 3.56, 95% CI: 1.62–7.83, P=0.002; no heterogeneity; moderate quality of evidence) (*Table 2*, *Figure 2B,C*). Our result does not conflict with recent RCT by Boulware (24), which demonstrated postexposure prophylactic HCQ did not prevent illness compatible with COVID-19 or confirmed infection (24).

HCQ and CQ are drugs with a wide range of anti-inflammatory, immunomodulatory, anti-malarial, anti-viral, and anti-tumor effects (25). Although their molecular

Table 2 Summary of finding table

	Study	Pt	OR or HR (95% CI)	P	I², P for heterogeneity	Quality of evidence	Reason for quality of evidence down grading
Primary outcome							
Death from any cause	7	1,925	OR: 1.05 (0.53–2.09)	0.89	31%, 0.18	Very low	Non-RCT, RoB
Time to viral clearance	4	352	HR: 1.19 (0.74–1.94)	0.47	57%, 0.07	Low	Non-RCT, RoB
Viral clearance at day 7	4	244	OR: 1.47 (0.33–6.63)	0.62	74%, <0.001	Very low	Non-RCT, RoB, imprecision, inconsistency
Secondary outcome							
Time to discharge	2	160	HR: 2.29 (0.72–7.27)	0.16	73%, 0.06	Very low	Non-RCT, RoB, imprecision
Time to symptom alleviation	1	150	HR: 1.01 (0.59–1.75)	0.97	NA	Moderate	RoB
Time to CT image improvement	1	22	HR: 2.42 (0.83–7.05)	0.10	NA	Very low	RoB, imprecision
CT image improvement at day 7	3	114	OR: 1.22 (0.28–5.29)	0.79	54%, 0.11	Very low	RoB, imprecision
Disease progression (death or ICU admission)	2	223	OR: 1.41 (0.28–7.05)	0.68	37%, 0.21	Very low	Non-RCT, RoB, imprecision
Any adverse event	3	242	OR: 3.56 (1.62–7.83)	0.002	0%, 0.51	Moderate	RoB
Serious adverse event	3	242	OR: 2.11 (0.27–16.68)	0.48	0%, 0.74	Low	RoB, imprecision

Quality of evidence was graded into four ranks: high, moderate, low, and very low according to GRADE guidelines. Non-RCT: including observational study; RoB: high risk of bias; imprecision: wide 95% CI of the pooled value. Inconsistency: significant heterogeneity. OR, odds ratio; HR, hazard ratio; 95% CI, 95% confidence interval; RCT, randomized controlled trial; ICU, intensive care unit.

mechanisms are not clear, inhibition of autophagy and Toll-like receptor function have been reported. CQ has been shown to have *in vitro* activity against multiple RNA viruses including SARS-CoV-1 (26). It has also been noted that HCQ and CQ may inhibit sialic acid synthesis, protein glycosylation, and the cellular interactions involved in viral attachment and invasion (27,28).

From our meta-analysis, in addition to the lack of a convincing therapeutic effect, there was a significant increase in any adverse events, but not for the severe adverse events (*Figure 2D*). HCQ and CQ are generally well-tolerated medications, but clinicians and patients should be aware of the serious adverse events that can occur, even during short courses of the treatment. Notorious harmful events include prolongation of the QT interval, which can cause arrhythmic death. While HCQ alone did not increased death compared to "neither of them" arm in the Rosenberg's observation, HCQ + AZM led to increased death compared to AZM alone. Abnormal electrocardiogram finding was noted in as many as 27.1% of patients with HCQ + AZM (*Table 2*) (23). Particular

attention should be paid to arrhythmia high-risk patients and the concomitant use of AZM because both AZM and HCQ independently cause QT prolongation (29). A recent phase IIb RCT in Brazil that compared high- and low-dose HCQ for COVID-19 cases was prematurely halted because frequent QT prolongation and increased lethality were observed in the high-dose arm of 12 g/day for 10 days (30). Transient gastrointestinal adverse events including diarrhea, abdominal pain, and abnormal liver function were also commonly observed in RCTs (9-12). Other side effects including rash, itchiness, and retinal damage have also been reported (9-12,31).

Both HCQ and CQ have been employed successfully for the treatment of SLE and RA over 70 years (32). All patients with SLE of any degree and type of disease activity should be treated with HCQ or CQ, unless these agents are contraindicated (33). Specially, HCQ has a good reputation for controlling erythematosus. A prolonged shortage of HCQ and CQ, which would like to be produced by widespread administration of HCQ and CQ for COVID-19, will deprive people with SLE and RA of an

effective, well-tolerated, and low-cost drugs. Patients and rheumatologists are terrified that they might lose access to their key drugs, further threatening disease progression and quality of living (8).

Currently, we do not have any treatment option or vaccination verified by large-scale trials; despite the need for swift action to stop this catastrophic pandemic. Many people tend to jump at any attractive information, despite the very low quality of clinical evidence provided by small-scale observational studies or *in vitro* experiments. The global COVID-19 pandemic has also exerted pressure on clinicians and regulatory authorities to act quickly to provide effective drugs to patients. Some groups have argued that the authorities should promptly approve a drug without any RCT data (5,6,34). Based on limited *in vitro* and anecdotal clinical data from case series, HCQ and CQ are currently recommended for the treatment of hospitalized COVID-19 patients in several countries (6). For example, a Chinese expert panel recommended oral CQ, 500 mg twice per day for 10 days for patients diagnosed with mild, moderate, and severe COVID-19 cases without scrutinizing the clinical evidence (2). The US FDA approved the prescription of HCQ and CQ for hospitalized patients and is facilitating the availability of HCQ and CQ during the COVID-19 pandemic to treat as many patients as possible who are not eligible for a clinical trial (5,6). Despite warnings from scientific advisers, the FDA adopted this policy based on a single, small observational study showing that HCQ treated COVID-19 patients experienced prompt viral load clearance (4). This faster viral clearance in HCQ arm was not confirmed by subsequent RCTs (*Figure 2B,C*). These unprecedented policy-making processes are contrary to the foundation of evidence-based medicine (35). Non-evidence based medical policy decisions put the patient safety and drug reviewing system at risk, which requires "substantial evidence" of safety and efficacy based on well-controlled and well-designed trials before a drug can be marketed (34).

We would like to comment on the possible advantages from HCQ/CQ treatment. Administration of CQ was associated with trend toward shorter hospital stay (HR: 2.29, 95% CI: 0.72–7.27, P=0.16) (11,13) (Figure S1). Our analysis was not able to completely refute this possible therapeutic merit. If quicker recovery can be achieved by HCQ or CQ, this would greatly improve the crisis of medical resource shortage. Future RCTs may confirm this clinical benefit of HCQ.

Limitations of our analysis should also be mentioned. First, all the included studies had considerable methodological weaknesses leading to certain high risk of bias, primarily due to the non-randomized study designs and a lack of blinding. Second, pooled statistics for many outcomes were compromised by the small number of studies and patients. Therefore, the quality of evidence for each outcome is not high (*Table 2*). Third, the majority of COVID-19 patients in our analysis had asymptomatic, mild, or moderate disease; thus, external validity of our analysis for severe and critical cases is weak. Finally, our systematic review did not evaluate combination of HCQ/CQ with other antiviral medications. Despite these considerable limitations, we offer our analysis as a response to the urgent need for the summarized data for HCQ/CQ treatment on COVID-19.

In conclusion, based on the available evidence, the routine administration of HCQ/CQ for COVID-19 patients is not recommended (weak recommendation, Grade 2C). This treatment is associated with an increased risk of adverse events without any conclusive clinical benefit including faster viral clearance. Although the currently available evidence is not yet conclusive, numerous relevant RCTs have been listed on the trial registration website (36). We hope that these trials and additional systematic reviews will update the evidence regarding this important topic.

Footnote

Reporting Checklist: The authors have completed the PRIMSA reporting checklist. Available at http://dx.doi.org/10.21037/jtd-20-2022

Peer Review File: Available at http://dx.doi.org/10.21037/jtd-20-2022

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-2022). TK received a lecture fee from Sanofi in Japan. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Appendix 1 Search formulas

PubMed

(ncov OR covid OR 2019-nCoV OR COVID-19 OR (wuhan and coronavirus) OR sars-cov OR (2019 novel coronavirus)) AND (chloroquine or hydroxychloroquine)

Web of Science

TS = (ncov OR covid OR 2019-nCoV OR COVID-19 OR (wuhan and coronavirus) OR sars-cov OR (2019 novel coronavirus)) AND TS = (chloroquine or hydroxychloroquine)

Embase

(ncov OR covid OR '2019 ncov' OR 'covid 19'/exp OR 'covid 19' OR (wuhan AND ('coronavirus'/exp OR coronavirus)) OR 'sars cov'/exp OR 'sars cov' OR '2019 novel coronavirus'/exp OR '2019 novel coronavirus' OR (2019 AND novel AND ('coronavirus'/exp OR coronavirus))) AND ('chloroquine'/exp OR chloroquine OR 'hydroxychloroquine'/exp OR hydroxychloroquine)

Cochrane

#1 ncov OR covid OR sars-cov OR novel coronavirus
#2 chloroquine or hydroxychloroquine
#3 #1 and #2

MedRxiv

chloroquine or hydroxychloroquine
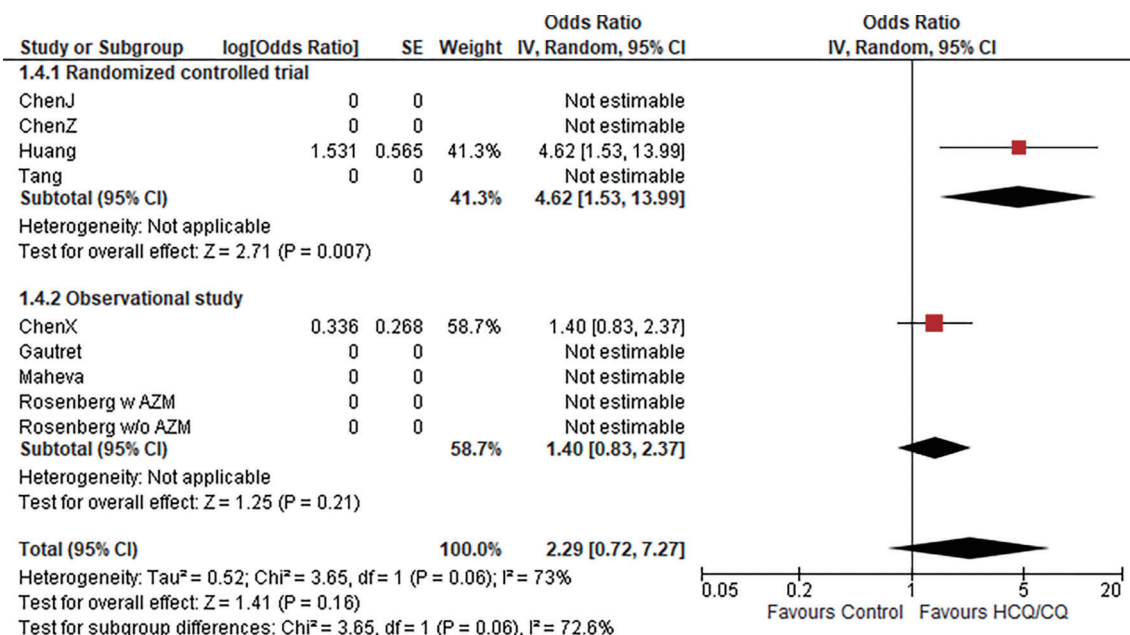
Figure S1 A forest plot for time to discharge. Rosenberg w AZM (with AZM): "HCQ + AZM versus AZM alone". Rosenberg w/o AZM (without AZM): "HCQ alone versus neither of them". SE, standard error; 95% CI, 95% confidence interval; IV, inverse variance; M-H, Mantel-Haenszel; HCQ/CQ, hydroxychloroquine/chloroquine; AZM, azithromycin.
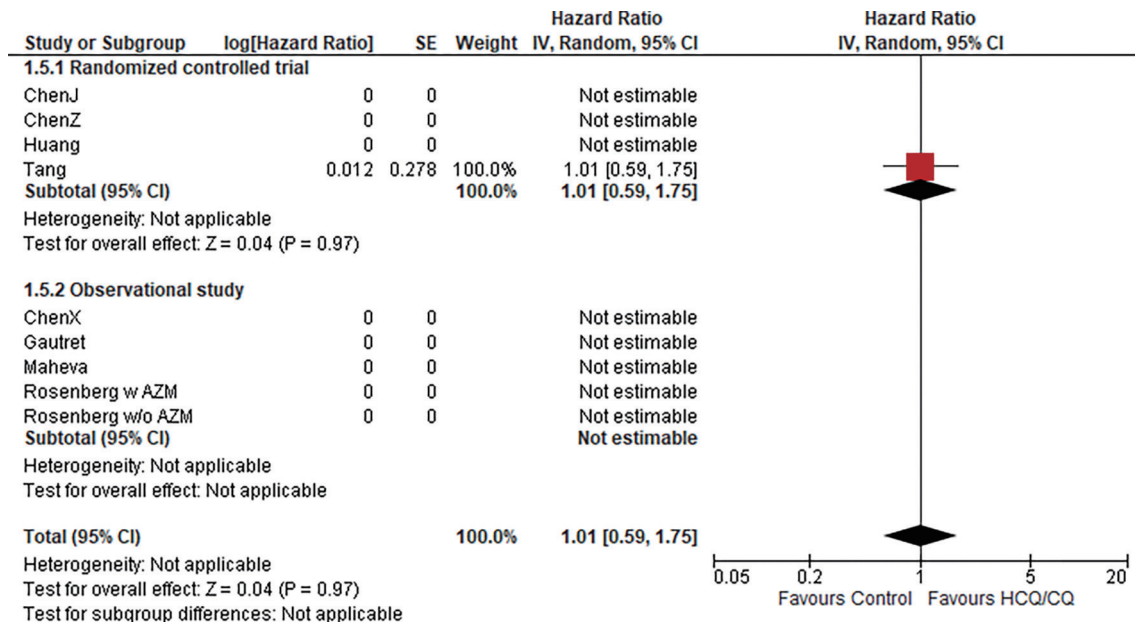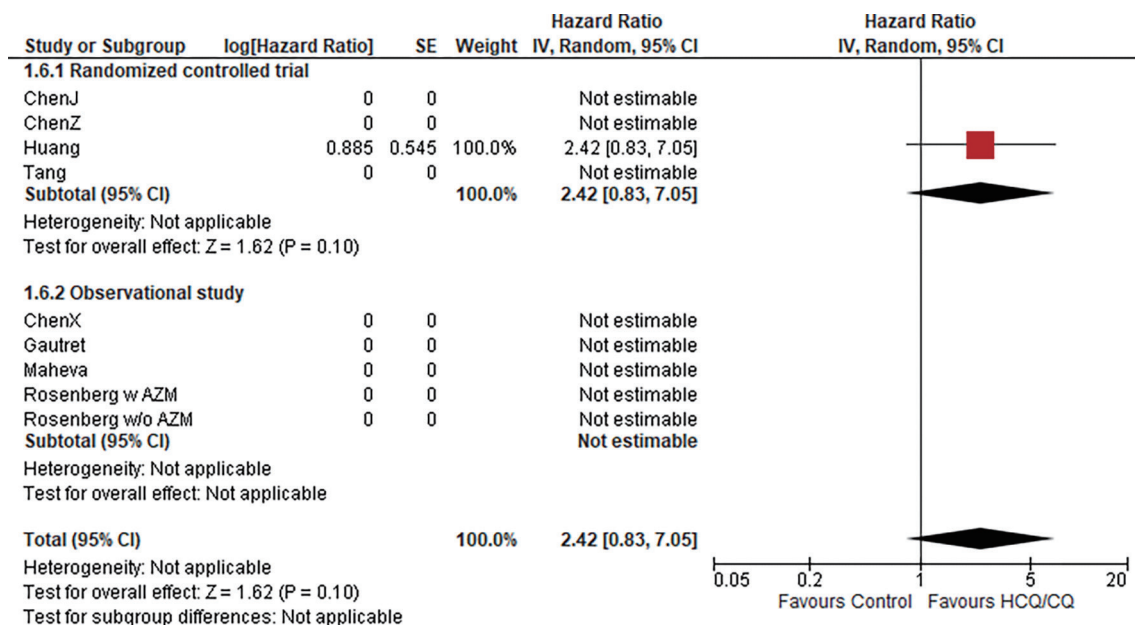
Figure S2 A forest plot for time to symptom alleviation. Rosenberg w AZM (with AZM): "HCQ + AZM versus AZM alone". Rosenberg w/o AZM (without AZM): "HCQ alone versus neither of them". SE, standard error; 95% CI, 95% confidence interval; IV, inverse variance; M-H, Mantel-Haenszel; HCQ/CQ, hydroxychloroquine/chloroquine; AZM, azithromycin.
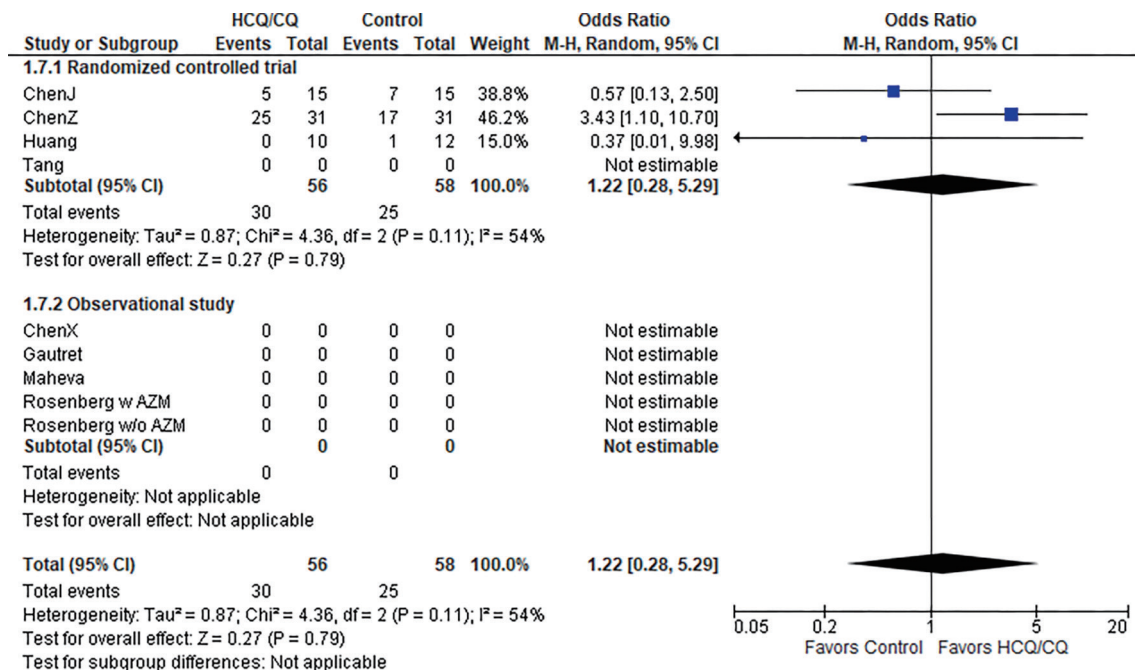

Figure S3 A forest plot for time to CT image improvement. Rosenberg w AZM (with AZM): "HCQ + AZM versus AZM alone". Rosenberg w/o AZM (without AZM): "HCQ alone versus neither of them". SE, standard error; 95% CI, 95% confidence interval; IV, inverse variance; M-H, Mantel-Haenszel; HCQ/CQ, hydroxychloroquine/chloroquine; AZM, azithromycin.
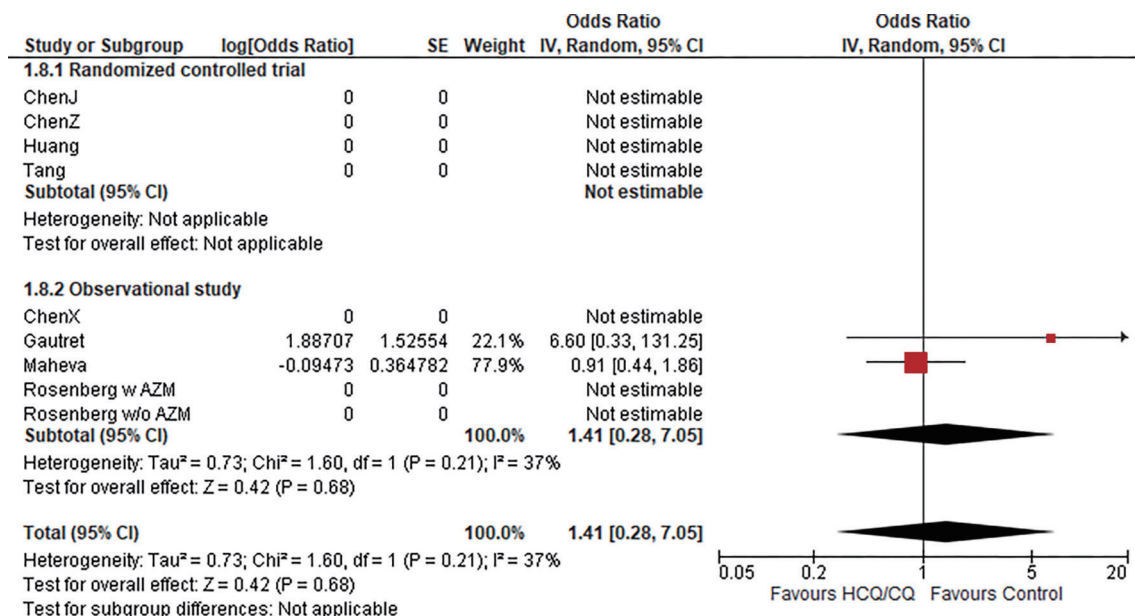
Figure S4 A forest plot for CT image improvement at day 7. Rosenberg w AZM (with AZM): "HCQ + AZM versus AZM alone". Rosenberg w/o AZM (without AZM): "HCQ alone versus neither of them". SE, standard error; 95% CI, 95% confidence interval; IV, inverse variance; M-H, Mantel-Haenszel; HCQ/CQ, hydroxychloroquine/chloroquine; AZM, azithromycin.

Figure S5 A forest plot for disease progression (death or intensive care unit admission). Rosenberg w AZM (with AZM): "HCQ + AZM versus AZM alone". Rosenberg w/o AZM (without AZM): "HCQ alone versus neither of them". SE, standard error; 95% CI, 95% confidence interval; IV, inverse variance; M-H, Mantel-Haenszel; HCQ/CQ, hydroxychloroquine/chloroquine; AZM, azithromycin.
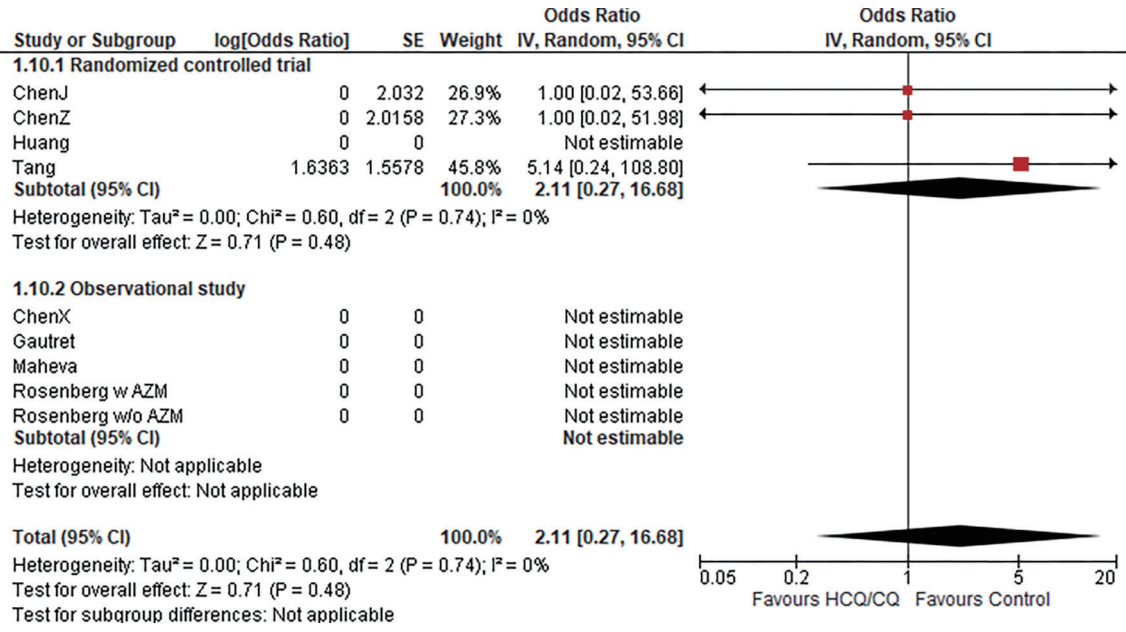
Figure S6 A forest plot for serious adverse event. Rosenberg w AZM (with AZM): "HCQ + AZM versus AZM alone". Rosenberg w/o AZM (without AZM): "HCQ alone versus neither of them". SE, standard error; 95% CI, 95% confidence interval; IV, inverse variance; M-H, Mantel-Haenszel; HCQ/CQ, hydroxychloroquine/chloroquine; AZM, azithromycin.
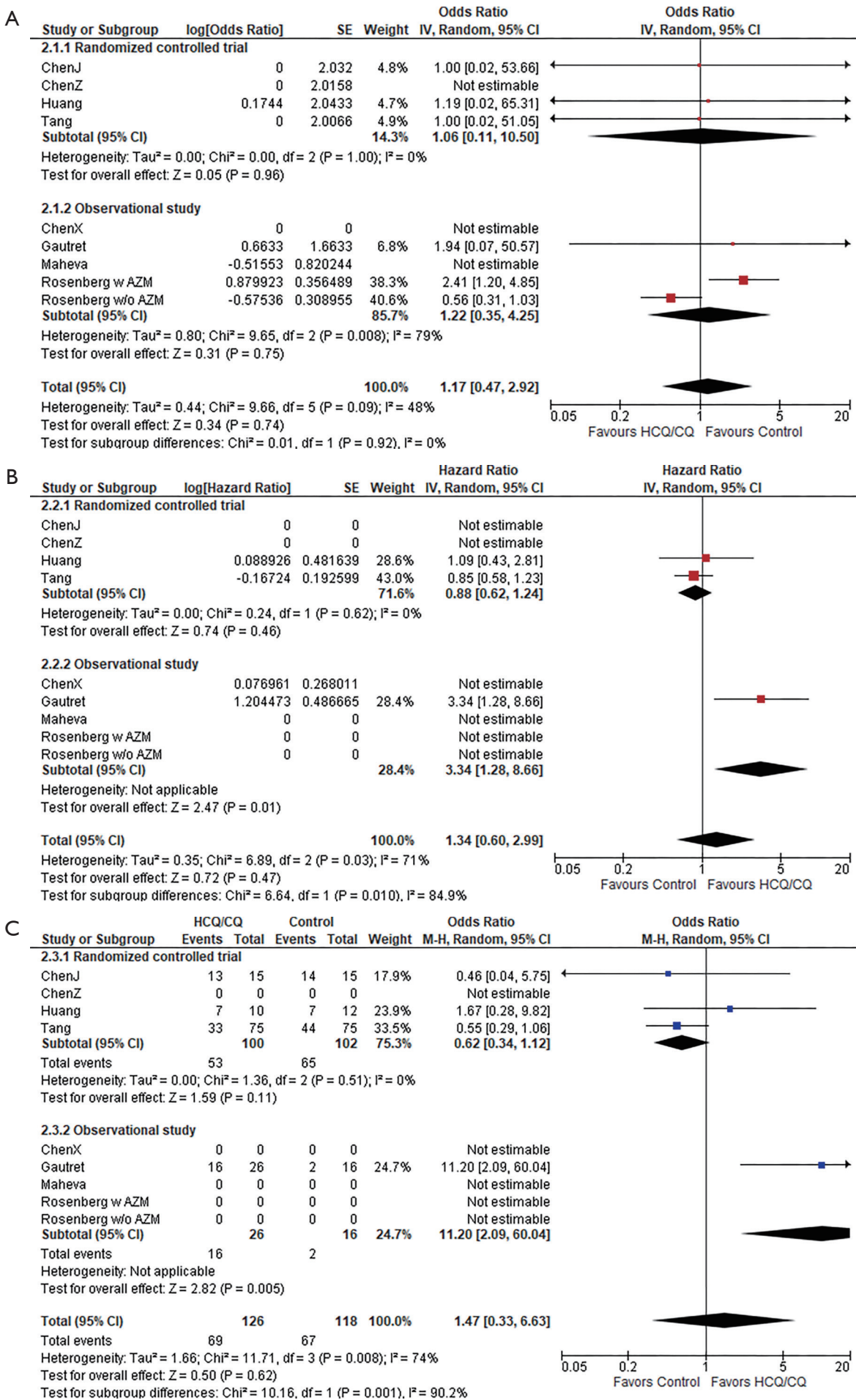

Figure S7 A forest plot for primary outcomes excluding non-peer reviewed articles. (A) All cause death; (B) time to viral clearance; (C) viral clearance at day 7. Rosenberg w AZM (with AZM): "HCQ + AZM versus AZM alone". Rosenberg w/o AZM (without AZM): "HCQ alone versus neither of them". SE, standard error; 95% CI, 95% confidence interval; IV, inverse variance; M-H, Mantel-Haenszel; HCQ/CQ, hydroxychloroquine/chloroquine; AZM, azithromycin.