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Review Article

Efficacy and safety of chloroquine and hydroxychloroquine for treatment of COVID-19 patients-a systematic review and meta-analysis of randomized controlled trials

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Abstract: The coronavirus disease 19 (COVID-19) pandemic has caused significant morbidity and mortality worldwide and an effective treatment is needed. Chloroquine (CQ) and hydroxychloroquine (HCQ) have shown in vitro antiviral activity against SARS-CoV-2 which causes the disease, but the evidence from in vivo studies so far has been inconclusive. Objective: To evaluate the efficacy and safety of CQ and HCQ in the treatment of COVID-19. Data Sources: We systematically searched the PubMed, Embase, MEDLINE, Cochrane CENTRAL, CINAHL, Scopus, Joanna Briggs Institute Database, ClinicalTrials.gov, and Chinese Clinical Trial Registry (ChiCTR) for all articles published between 01 January 2020 to 15 September 2020 on CQ/HCQ and COVID-19 using a predefined search protocol; without any language restrictions. A search of grey literature repositories (New York Academy of Medicine Grey Literature and Open Grey), and pre-publication server deposits (medRxIV and bioRxIV) was also performed. Study Selection: Randomized clinical trials (RCT) which compared CQ/HCQ to standard supportive therapy in treating COVID-19 were included. Data Extraction and Synthesis: Data were extracted from original publications by four independent reviewers. Risk of bias was assessed using the Cochrane Collaboration's assessment tool. Data were meta-analyzed using a random-effect models. Results are reported according to PRISMA guidelines. Main Outcome(s) and Measure(s): The primary prespecified efficacy outcome was all-cause mortality. The primary safety outcome was any adverse effect attributed to use of CQ/HCQ. Results: Eight RCTs were included and pooled in the mortality meta-analysis (6,592 unique participants; mean age = 59.4 years; 42% women). CQ/HCQ did not show any mortality benefit when compared to standard supportive therapy (Pooled Relative Risk [RR] 1.07; 95% CI = 0.97-1.18; I^2 statistic = 0.00%). Sensitivity and sub-group analyses showed similar findings. Any adverse event was significantly higher in patients randomized to CQ/HCQ (RR = 2.51; 95% CI = 1.53-4.12; n = 1,818 patients), but the risk of developing severe adverse event was not statistically significant (RR = 0.99, 95% CI = 0.53-1.86; n = 6,456 patients). Conclusions and Relevance: Evidence from currently published RCTs do not demonstrate any added benefit for the use of CQ or HCQ in the treatment of COVID-19 patients.

Keywords: COVID-19, SARS-CoV-2, hydroxychloroquine, chloroquine, randomized controlled trials, systematic review, meta-analysis

Introduction

The ongoing global pandemic of Coronavirus Disease 19 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) presently accounts for more than 56 million cases with over 1,600,000 deaths across 188 countries/regions [1]. To contain the pandemic, several countries implemented social restrictions that resulted in an unprecedented global shutdown with huge psychosocial, economic, and political implications. Hence, the urgent need for an effective treatment and/or prophylaxis for this disease.

Chloroquine (CQ) and hydroxychloroquine (HCQ) are among the drugs that have gained attention as potential treatment options for COVID-19 [2].

For over eight decades, CQ has been used for the treatment and prophylaxis of malaria and chronic rheumatoid conditions, whereas its less toxic (about 40% less toxic) hydroxyl analogue, HCQ, has mainly been reserved for treating connective tissue disorders including systemic lupus erythematosus and rheumatoid arthritis [2]. Both drugs have anti-inflammatory, immunomodulatory, and antiviral properties [3-6]. CQ is a potent inhibitor of the SARS Coronavirus (SARS-CoV) and SARS-CoV-2 in *in vitro* studies [2, 6-9], and has been suggested to exhibit antiviral activity against Zika virus, poliovirus, HIV, and influenza viruses A & B [3, 10-12]. Despite potent in-vitro efficacy of CQ and HCQ on SARS-CoV-2, lethal side effects such as hypoglycaemia and prolongation of the QTc interval have raised safety concerns for their widespread use in this pandemic [13-15], especially when used in combination with other QT prolonging antimicrobials. Nevertheless, given their extensive clinical use for malaria, rheumatoid and autoimmune disorders, anecdotal evidence suggest that CQ and HCQ are generally safe and well-tolerated [2, 6, 14, 15]. Early promising results from clinical trials in France and China prompted research interests in the clinical efficacy of CQ and HCQ for the treatment and prophylaxis for COVID-19 infection [16-18]. Thus, several studies evaluating the efficacy and safety of CQ and HCQ use in COVID-19 patients were conducted using various designs that include observational, non-randomized controlled trials (non-RCTs), and randomized controlled trials (RCTs). Previous systematic reviews of these studies [18-24] show inconsistent findings related to the efficacy of CQ/HCQ in COVID-19 patients, which may be explained in part by the heterogeneous designs and varied levels of methodological rigour among the included studies [18, 25, 26].

Pooling evidence from RCTs will provide the highest level of evidence on the efficacy and safety of CQ and HCQ in COVID-19 patients. Hence, we conducted a systematic review with meta-analysis of published and unpublished trials to evaluate the efficacy of CQ and HCQ on a broad range of clinical outcomes when used alone or in combination with other drugs in treating COVID-19 patients. We also aimed to evaluate the safety of CQ and HCQ in these patients.

Methods

The protocol for this systematic review was developed according to PRISMA guidelines [27], and prospectively registered in an International register of systematic reviews: PROSPERO CRD42020209075.

Inclusion criteria

We included articles in any language that met the eligibility criteria based on the PICOS strategy: (1) Population (P): Patients diagnosed with COVID-19, including all ranges of severity (mild, moderate, and severe), all ethnic groups, and all age groups. We excluded patients not diagnosed with COVID-19, and patients being given CQ or HCQ for prophylaxis. (2) Intervention (I): Interventions in which CQ or HCQ was used in the treatment of COVID-19 patients. We excluded studies in which patients received CQ or HCQ as prophylaxis. (3) Comparison (C): compared with standard/usual care provided as per existing protocol in the trial hospital or country. We excluded studies in which CQ or HCQ was in the control/comparator arm. (4) Outcome (O): Relevant outcomes included all-cause mortality; Clinical deterioration (defined as progression from mild/moderate to severe disease requiring hospitalization with or without supplemental oxygen but excluding death); time to clinical recovery (defined as the duration from COVID-19 diagnosis to complete resolution of clinical symptoms); time to negative PCR (defined as the amount of time for seroconversion from positive to negative COVID-19 PCR test); length of stay in hospital; and safety including adverse events (defined as the onset of a new symptom or worsening of a pre-existing condition after randomization) and serious adverse events (defined as any adverse event that resulted in hospitalization or death after randomization). (5) Study design (S): published and unpublished randomized controlled trials. Observational studies and non-RCTs were excluded.

Search strategy

We searched the National Library of Medicine, Embase, MEDLINE, Cochrane CENTRAL, CIN-

AHL, Scopus, Joanna Briggs Institute Database, ClinicalTrials.gov, and Chinese Clinical Trial Registry (ChiCTR) for eligible studies published between 01 January 2020 and 15 September 2020. Search terms included hydroxychloroquine, hydroxychloroquine sulphate, chloroquine, chloroquine phosphate, chloroquine diphosphate, clinical trial, and randomized controlled trial. We also searched grey literature websites (e.g. New York Academy of Medicine Grey Literature and Open Grey) and pre-publication server deposits (e.g. medRxIV and bioRxIV). Additionally, we sought relevant articles from the references of studies identified through the database search. There was no language restriction and non-English studies were translated into English using a translation service.

Data extraction

Data on participants' demographic and clinical characteristics were retrieved using a data extraction form, including age; sex; ethnicity; country of origin; pre-existing comorbidities (e.g. CAD, CHF, arrhythmia, hypertension, diabetes, dyslipidaemia, COPD, CKD, liver diseases, cancer, and immune system disorders); smoker status (e.g. ever smokers, never smokers); regular medications (e.g. anticoagulants, ACE inhibitors, ARBs, statins, antivirals); and COVID-19 severity. We also extracted the data on the study outcomes for each treatment arm.

Risk of bias assessment

Two reviewers independently performed risk of bias assessments using the Cochrane Collaboration's Tool for assessing risk of bias in five domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (income outcome data reporting), and reporting bias (selective reporting) [28]. If any of the five domains was found to be associated with some concerns of risk of bias or high risk of bias, the overall risk of bias was rated as 'some concern' or 'high risk', respectively. Otherwise, the RCT was rated as 'low risk'. Any discrepancies in these assessments were resolved by discussion with a third reviewer.

Data synthesis

Descriptive statistics and narrative synthesis were used to summarize the characteristics of included studies. Pairwise meta-analysis using the conventional random-effects model were performed to pool individual results. Sensitivity and subgroup analyses were performed for the primary study outcome (all-cause mortality). Risk ratios (RR) and 95% confidence interval (CI) were estimated for categorical outcomes, and mean differences (MD) and 95% CI for continuous outcomes. Analyses were conducted using Stata version 16.1 (STATA Corp, College Station, TX).

Results

Selection of studies

Our search yielded a total of 1,639 studies, of which 387 duplicates were removed, leaving 1,252 studies. After screening by titles and abstracts, a further 1,232 studies were excluded, leaving 20 full-text articles for review. Eleven of these 20 studies met inclusion criteria [29-39], while the remaining nine studies were excluded for the following reasons: use of CQ or HCQ for prophylaxis [40-42], non-RCTs and quasi-randomized trials [16, 43, 44], the comparator arm was not usual care or placebo [45, 46], and pre-print of a published study that already met inclusion criteria [31]. The study selection process is illustrated in a PRISMA flow diagram (**Figure 1**).

Description of included RCTs

Eleven RCTs, presented in **Table 1**, include six peer-reviewed published studies and five pre-prints comprising a total of 7,184 patients (Mean age = 57.6 years, SD = 18.5 years, 39.6% women) across nine countries. The most recent study, Abd-Elsalam et al., 2020 was published on 14 August 2020 [29]. Nine RCTs were open-label RCTs and the other two were double-blinded studies. Efficacy and safety of HCQ in COVID-19 patients was evaluated in all 11 RCTs, HCQ in combination with Azithromycin in one RCT, and CQ alone in one RCTs. Participants in the RCTs were patients with mild COVID-19 in three RCTs [35, 37, 38], mild-to-moderate patients in four RCTs [30-32, 39], patients with moderate COVID-19 symptoms in one RCT [33],

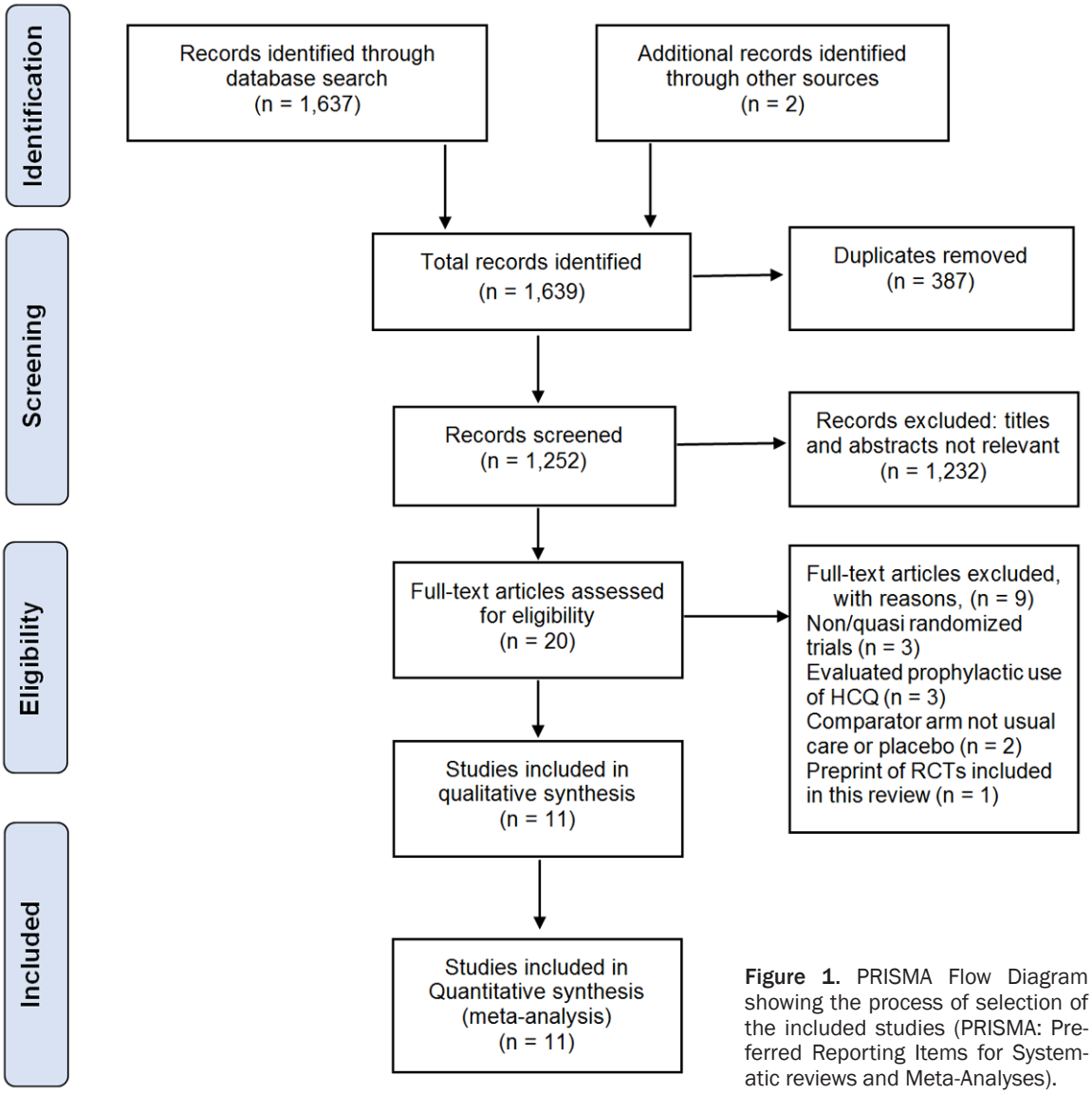

Figure 1. PRISMA Flow Diagram showing the process of selection of the included studies (PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses).

moderate-to-severe COVID-19 patients in one RCTs [34], and all severity of COVID-19 in two RCTs [29, 36]. Based on different study endpoint periods, included RCTs evaluated outcomes on mortality, viral clearance, improvement of clinical status, time to clinical recovery (TTCR), utilization of mechanical ventilation and adverse events due to the use of CQ alone, HCQ alone, or HCQ in combination with Azithromycin.

Risk of bias assessment

Table 2 describes the risks of bias in the included RCTs. Of the 11 RCTs included in this study, 10 were assessed to have a high risk of bias in one or more domains [29-34, 36-39], and one RCTs was assessed to have a low risk of bias across all domains [35]. Of note, analyses were intention-to-treat (ITT) in eight of the 11 RCTs, hence attrition bias was deemed to be low risk in these studies [29-31, 33, 35-38].

Mortality

Eight RCTs [29-32, 36, 38, 39] compared mortality outcomes among 6,592 patients (Mean = 59.4 years, SD = 17.9 years, 42% women) randomized to CQ/HCQ or control arms. Of note, all deaths occurred within 28 days of COVID-19 diagnosis. The pooled results showed no significant difference in mortality rates between

Table 1. Summary of RCTs evaluating use of CQ and HCQ for treatment of COVID-19 patients

Study, Publication status	Trial Registry Identifier	Country	Design	No. of Participants	Participants	Study (trial) arms	Outcomes
Abd-Elsalam et al., 2020; *Published*	NCT04353336	Egypt	RCT, Open label	194	Severity: Mild, moderate, and severe Age, Mean ± SD: 40.7 ± 19.3 yrs Sex, Female: 41.2%	Arm 1: HCQ Arm 2: Usual care (Control group)	Primary 1). Clinical recovery 2). Need for mechanical ventilation 3). Mortality within 28 days Secondary Adverse/Side effects
Cavalcanti et al., 2020; *Published*	NCT04322123	Brazil	RCT, Open label	667	Severity: Mild to moderate Age, Mean ± SD: 50.3 ± 14.6 yrs Sex, Female: 41.7%	Arm 1: HCQ and Azithromycin Arm 2: HCQ alone Arm 3: Usual care (Control)	Primary Clinical status on Day 15 Secondary 1). Clinical status at 7 days 2). An indication for intubation within 15 days 3). Receipt of supplemental oxygen between randomization and 15 days 4). Duration of hospital stay 5). In-hospital death
C. Chen et al., 2020; *Preprint*	NCT04384380	Taiwan	RCT, Open label	33	Severity: Mild to moderate Age, Mean ± SD: 32.9 ± 10.7 yrs Sex, Female: 42.4%	Arm 1: HCQ Arm 2: Usual care (Control)	Primary Time to negative rRT-PCR assessments from randomization up to 14 days Secondary 1). Proportion of negative viral PCR on Day 14 2). Time to clinical recovery 3). Proportion of discharges by Day 14 4). Mortality rate 5). Safety and tolerability
J. Chen et al., 2020; *Published*	NCT04261517	China	RCT, Open label	30	Severity: Moderate Age, Mean ± SD: 48.6 ± 3.6 yrs Sex, Female: 30%	Arm 1: HCQ Arm 2: Usual care (Control)	Primary Proportion of patients with negative rRT-PCR in pharyngeal swab on Day 7 Secondary 1). Occurrence of severe drug toxicity
L. Chen et al., 2020; *Preprint*	ChiCTR2000030054	China	RCT, Open label	48	Severity: Moderate to severe hospitalized Age, Mean ± SD: 46.9 ± 14.6 yrs Sex, Female: 54.2%	Arm 1: CQ Phosphate Arm 2: HCQ Arm 3: Usual care	Primary Time to clinical recovery Secondary 1). Time to negative rRT-PCR assessments 2). Length of hospital stay 3). Duration (days) of supplemental oxygenation 4). Adverse events 5). All-cause mortality
Z. Chen et al., 2020; *Preprint*	ChiCTR2000029559	China	RCT, double blind	62	Severity: Mild hospitalized Age, Mean ± SD: 44.7 ± 15.3 yrs Sex, Female: 53.2%	Arm 1: HCQ Sulphate Arm 2: Usual care (Control)	Primary Time to clinical recovery Secondary Adverse effects

Horby et al., 2020; *Preprint*	NCT04381936	UK	RCT, Open label	4,716	Severity: Mild, moderate, and severe hospitalized Age, Mean ± SD: 65.3 ± 15.3 yrs Sex, Female: 38.8%	Arm 1: HCQ Arm 2: Usual care (Control)	Primary All-cause mortality by Day 28 Secondary 1). Time to discharge from hospital and 2). Invasive mechanical ventilation 3). Cause-specific mortality 4). Major cardiac arrhythmia (recorded in a subset), 5). Receipt and duration of ventilation.
Kamran et al., 2020; *Preprint*	NCT04491994	Pakistan	RCT, Open label	500	Severity: Mild Age, Mean ± SD: 35.9 ± 11.2 yrs Sex, Female: 6.8%	Arm 1: HCQ Arm 2: Usual care (Control)	Primary Clinical progression of disease as per WHO criteria Secondary PCR negativity on Day 7 and Day 14
Mitja et al., 2020; *Published*	NCT04304053	Spain	RCT, Open label	293	Severity: Mild non-hospitalized Age, Mean ± SD: 41.7 ± 12.5 yrs Sex, Female: 68.6%	Arm 1: HCQ Arm 2: Usual care (Control)	Primary Reduction of viral RNA load in nasopharyngeal swabs at day 3 and day 7 after treatment start Secondary 1). Clinical progression up to 28 days 2). TTCR of symptoms within 28 days 3). Adverse events up to Day 28
Skipper et al., 2020; *Published*	NCT04308668	US, Canada	RCT, double blind	491	Severity: Mild to moderate non-hospitalized Age, Median (IQR): 40.0 (32 to 50) yrs Sex, Female: 56%	Arm 1: HCQ Arm 2: Placebo (Control)	Primary 1). Presence and severity of COVID-19 symptoms 2). Hospitalization status Secondary 1). Medication adherence 2). Adverse effects
Tang et al., 2020; *Published*	ChiCTR2000029868	China	RCT, Open label	150	Severity: Mild to moderate hospitalized Age, Mean ± SD: 46.1 ± 14.7 yrs Sex, Female: 45%	Arm 1: HCQ Arm 2: Usual care (Control)	Primary 1). Negative conversion of SARS-CoV-2 by Day 28 2). Clinical improvement in severity symptoms by Day 28 Secondary 1). Alleviation of clinical symptoms 2). All-cause mortality 3). Disease progression in patients

Table 2. Summary of risks of bias assessment using the Cochrane collaboration risk of bias assessment tool

Study	Doman 1: Selection bias *Random sequence generation*	Domain 1: Selection bias *Allocation concealment*	Domain 2: Performance bias *Blinding of participants & personnel*	Domain 3: Detection bias *Blinding of outcome assessment*	Domain 4: Attrition bias *Incomplete outcome data*	Domain 5: Reporting bias *Selective reporting*	Overall Judgement of Risk
Abd-Elsalam et al., 2020	Low risk	Unclear	High risk	High risk	Low risk	Low risk	High risk
Cavalcanti et al., 2020	Low risk	Low risk	High risk	High risk	High risk	Unclear	High Risk
C. Chen et al., 2020	Low risk	Low risk	High risk	High risk	Low risk	Low risk	High risk
J. Chen et al., 2019	Some concern	Some concern	High risk	High risk	Low risk	Low risk	High risk
L. Chen et al., 2020	Low risk	Unclear	High risk	High risk	High risk	Unclear	High risk
Z. Chen et al., 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Horby et al., 2020	Low risk	Low risk	High risk	High risk	Low risk	Low risk	High Risk
Kamran et al., 2020	Unclear	Unclear	High risk	High risk	Low risk	Low risk	High Risk
Mitja et al., 2020 A	Low risk	Low risk	High risk	High risk	Low risk	Low risk	High risk
Skipper et al., 2020	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	High risk
Tang et al., 2020	Low risk	Low risk	High risk	High risk	Low risk	Low risk	High risk

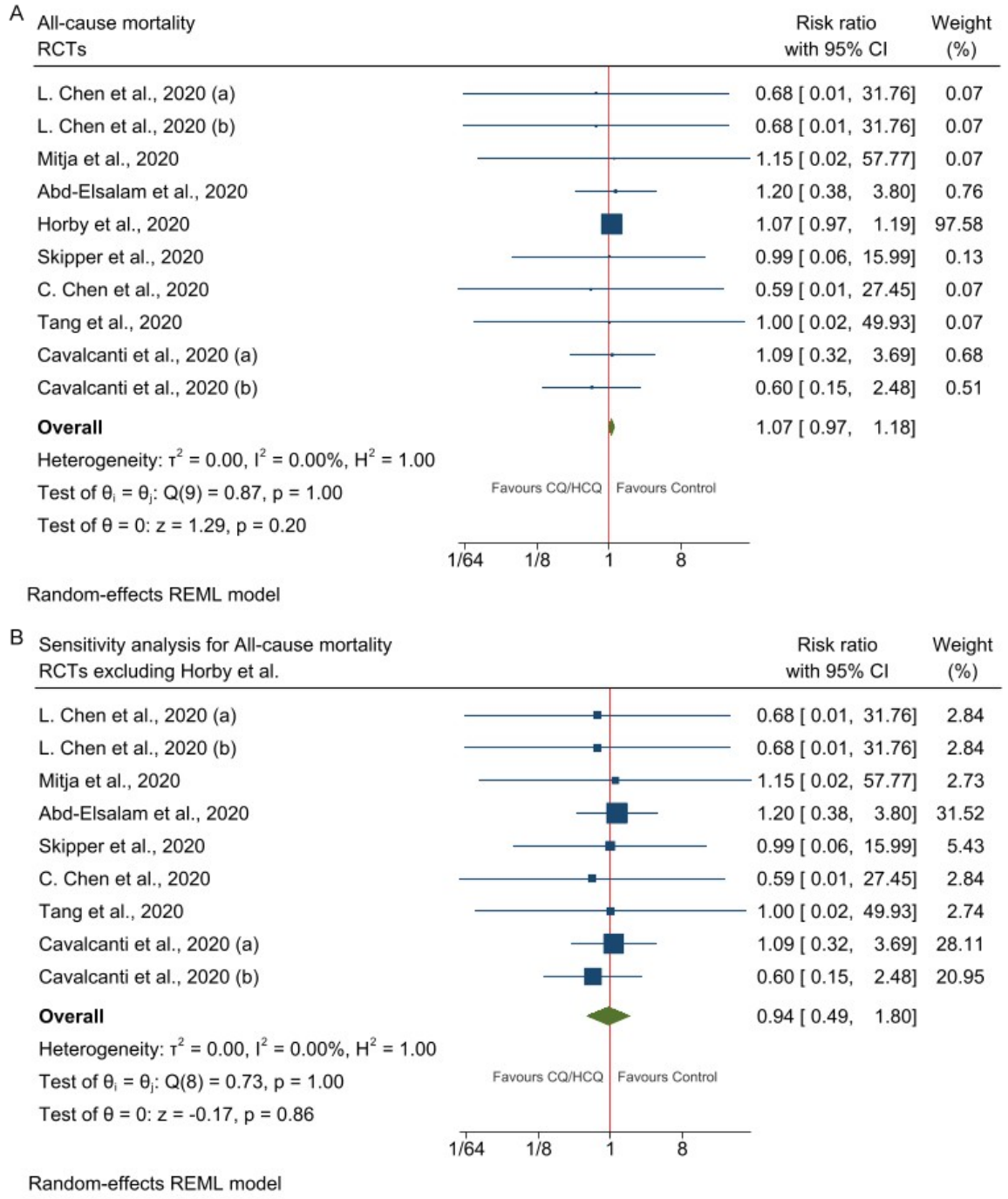

Figure 2. Forest plot of studies assessing mortality. A. All-cause mortality in patients randomized to CQ/HCQ vs Control (Usual care). B. Sensitivity analysis for all-cause mortality in patients randomized to CQ/HCQ vs Control (Usual care) excluding Horby et al., 2020. Legend: L. Chen et al., 2020 (a) represents the trials arm CQ vs Control; L. Chen et al., 2020 (b) represents the trials arm HCQ vs Control; Cavalcanti et al., 2020 (a) represents the trials arm HCQ vs Control; Cavalcanti et al., 2020 (a) represents the trials arm HCQ+ZAM vs Control.

treatment arms (RR = 1.07, 95% CI = 0.97-1.18) (**Figure 2A**). Given that Horby et al. [36] accounted for 97% of the combined weight of the eight RCTs, we performed a sensitivity analysis excluding this study from the meta-analysis. The pooled results excluding Horby et al. [36] also showed no statistically significant difference in mortality rates between HCQ/CQ and control [RR = 0.94, 95% CI = 0.49-1.80) (**Figure 2B**). Sub-group analysis showed mortality out-

Table 3. Sub-group analysis for mortality in included RCTs

Sub-group	No. of RCTs	Sample size	Pooled RR	95% CI	Comment(s)
Pharmacological agent					
CQ	1	30	0.68	0.01-31.76	P = 0.846
HCQ	8	6,513	1.07	0.97-1.19	I^2 statistic = 0.00%
HCQ+AZM	1	345	0.60	0.15-2.48	P = 0.485
Severity of COVID-19 patients					
Mild	1	635	1.15	0.02-57.74	P = 0.943
Mild to moderate	4	1,110	0.85	0.37-1.96	I^2 statistic = 0.00%
Moderate to Severe	1*	48	0.68	0.05-10.32	I^2 statistic = 0.00%
Mild, Moderate & Severe	2	4910	1.07	0.97-1.19	I^2 statistic = 0.00%
Duration of follow-up					
≤15 days	3	960	0.84	0.36-1.98	I^2 statistic = 0.00%
>15 days	5	5743	1.07	0.97-1.19	I^2 statistic = 0.00%

*Two comparisons: CQ vs Usual care and HCQ vs Usual care, of the same study were pooled together.

comes did not significantly vary with the pharmaceutical agent used (CQ vs HCQ vs HCQ+AZM), the categories of patients assessed (mild vs mild to moderate vs Moderate to severe vs All severity combined) nor with the duration of follow-up (≤ 15 days vs > 15 days) (**Table 3**).

Clinical deterioration excluding mortality

Data from eight RCTs [30, 33-39], including 6,630 patients showed no difference between CQ/HCQ and control in the proportions of patients who experienced deterioration of symptoms (RR 1.06, 95% CI = 0.90-1.26) (Supplementary Figure 1).

Time to clinical recovery

Data from four RCTs [29, 33-35] comprising 328 patients, showed that patients in the control arm recovered on average 8 hours earlier than patients in the CQ/HCQ arm, however this difference was not statistically significant (MD -0.34, 95% CI = -0.75-0.08) (Supplementary Figure 2).

Viral clearance

Five RCTs [29, 31-34] comprising data on 467 patients, compared the average time to negative PCR between HCQ/CQ and Usual Care. The results show that COVID-19 patients who received usual care achieved seroconversion approximately 11 hours earlier than patients who received HCQ/CQ, however the difference was not statistically significant (MD = -0.45, 95% CI = -1.02-0.11) (Supplementary Figure 3).

There was no difference in the viral load reduction between HCQ and controls on the 3rd day (mean reduction = -1.41 Log10 copies/mL, Standard Error (SE) = 0.15 vs mean reduction = -1.41 Log10 copies/mL, SE = 0.14) and on the 7th day (mean reduction = -3.44 Log10 copies/mL, SE = 0.18 vs mean reduction = -3.37 Log10 copies/mL, SE = 0.18) [38].

Length of stay in hospital

The mean duration of hospitalization did not differ between CQ/HCQ and control (MD = 0.03 (95% CI = -0.11-0.16, n = 698 patients)) [29, 30] (Supplementary Figure 4). Likewise, the proportions of patients discharged by the end of the study period were comparable between CQ/HCQ and control (RR 0.96, 95% CI = 0.93-1.00, n = 5,220 patients) [30, 36] (Supplementary Figure 5).

Safety

The risk of developing any adverse event was significantly higher in patients treated with CQ/HCQ than in those on usual care (RR = 2.25; 95% CI = 1.41-3.60; n = 1,818 patients) [30-35, 38, 39]-**Figure 3A**. However, the risk of developing serious adverse event (RR = 0.99, 95% CI = 0.53-1.86; n = 6,456 patients) [30-32, 35, 36, 38, 39] was the same in patients randomized to CQ/HCQ versus usual care (**Figure 3B**).

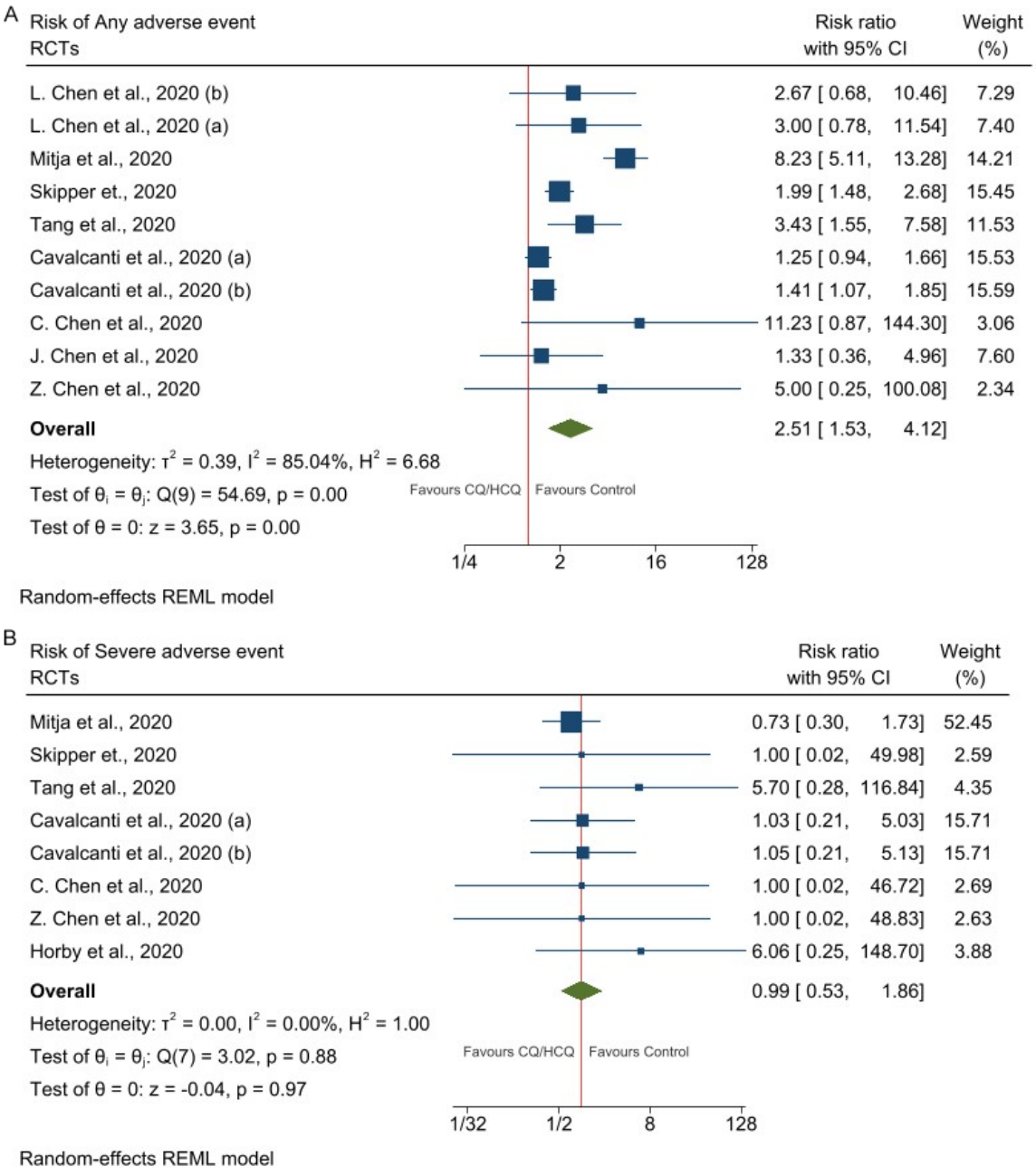

Figure 3. Forest plots of studies assess adverse events. A. Any adverse events in patients randomized to CQ/HCQ vs Control (Usual care). B. Severe adverse events in patients randomized to CQ/HCQ vs Control (Usual care). Legend: L. Chen et al., 2020 (a) represents the trials arm CQ vs Control; L. Chen et al., 2020 (b) represents the trials arm HCQ vs Control; Cavalcanti et al., 2020 (a) represents the trials arm HCQ vs Control; Cavalcanti et al., 2020 (a) represents the trials arm HCQ+ZAM vs Control.

The most frequent adverse events were transient, non-threatening insignificant treatment-related gastrointestinal (e.g., diarrhea, nausea, and abdominal pain) and nervous system disorders (e.g., drowsiness, headache, and metallic taste) [31, 34, 35, 38, 39]. Generally, patients who were randomized to HCQ-azithromycin combination reported a few more adverse events compared to patients who received HCQ alone [30]. Overall, CQ and HCQ were generally safe and well tolerated [31, 34, 38].

Electrocardiograph (ECG) monitoring for prolongation of QTc interval and serial cardiac

enzyme testing showed no evidence of CQ/HCQ-related cardiotoxicity [31, 34, 38]. However, QTc prolongation was more common in patients randomized to HCQ plus azithromycin combination or HCQ alone compared to patients randomized to usual care [30]. CQ did not cause any ECG changes or abnormal levels of cardiac enzymes, though patients with prior history of cardiac diseases were excluded in this study [34]. Concurrent use of CQ with other medications was not evaluated [34].

Discussion

Our meta-analysis demonstrated that there is no mortality benefit in treatment with chloroquine or hydroxychloroquine in either mild, moderate, or severe COVID-19 disease. Clinical recovery, viral clearance and duration of hospital stay did not differ between treatment groups and controls in pooled analysis. This is a frequent feature of respiratory viral infections which are usually mostly self-limiting and do not have effective treatments [47-49]. Previous observational data that showed benefit for chloroquine or hydroxychloroquine in the treatment of COVID-19 are likely affected by confounding and selection bias [50]. For example, the observational study from the Henry Ford Hospital in Detroit, Michigan reported benefit for patients who received hydroxychloroquine; however, a significant proportion of the patients in this study also received steroids, which were recently reported to benefit a subset of patients with COVID-19 [50-52]. Additionally, some observational data also do not demonstrate improved clinical outcomes for use of chloroquine or hydroxychloroquine further illustrating this issue of inconsistent selection bias and confounding [53].

Our study also showed that chloroquine and hydroxychloroquine did not significantly cause severe adverse events to the patients in the treatment groups compared to those treated with usual care or placebo. This aligns with reports of a good safety profile and low risk/benefit balance of these drugs especially with short term usage [54]. Although this finding may help assuage fears and lay credence to the persistent use by some health institutions in various countries who may not have access to other treatment options, our study does not demonstrate any obvious benefit in morbidity or hard outcomes.

Prevention efforts centered around viral transmission risk mitigation, case containment, and treatment efforts based on high quality supportive care are likely the most important key efforts that are currently available in limiting the morbidity and mortality from COVID-19 [55-57]. Novel mRNA vaccines have also shown promise for reducing severity of disease, and possibly reducing viral transmission in early clinical trials. As such, research efforts should be channeled towards these initiatives and other ongoing therapeutic options. Finally, future clinical trials evaluating CQ, HCQ and other potential drugs for COVID-19 should address methodological quality gaps identified in this review, recruit adequate sample size of participants including children and should preferably be multi-centric.

Strengths and limitations

Randomized controlled trials (RCTs) are the best study design to test the efficacy of interventions as they are not subject to known and unknown confounders [58, 59]. However, the extent to which their results can be extrapolated to a wider population is debatable because standardized and controlled study conditions may not always adequately reflect clinical reality [58, 59]. Notwithstanding, RCTs are considered the gold standard and our systematic review only shortlisted RCTs as this increases the internal validity of the findings.

Most RCTs included in our study utilized open-label randomization. As such, we cannot exclude the possibility of any residual confounding in these studies. However, recent study showed no difference in estimated treatment effect between trials with and without blinded patients, healthcare providers, or outcome assessors [60]. Few of the included RCTs had relatively small sample size so it is not impossible that a true therapeutic effect and difference may have been undetected. Although we included all eligible published and unpublished RCTs as of today in our study, our findings may not be considered conclusive since there are still other ongoing RCTs that are underway whose results are pending and have not been considered in our current meta-analysis. Albeit these limitations, our study summarizes the most recent and robust available RCTs at this time.

Conclusion

Evidence from currently published RCTs do not demonstrate any added benefit for the use of CQ or HCQ in the treatment of COVID-19 patients. Unless future clinicals trials prove otherwise, our findings suggest that research efforts should be directed towards other potential treatment options to control this and future coronavirus outbreaks.

Disclosure of conflict of interest

None.

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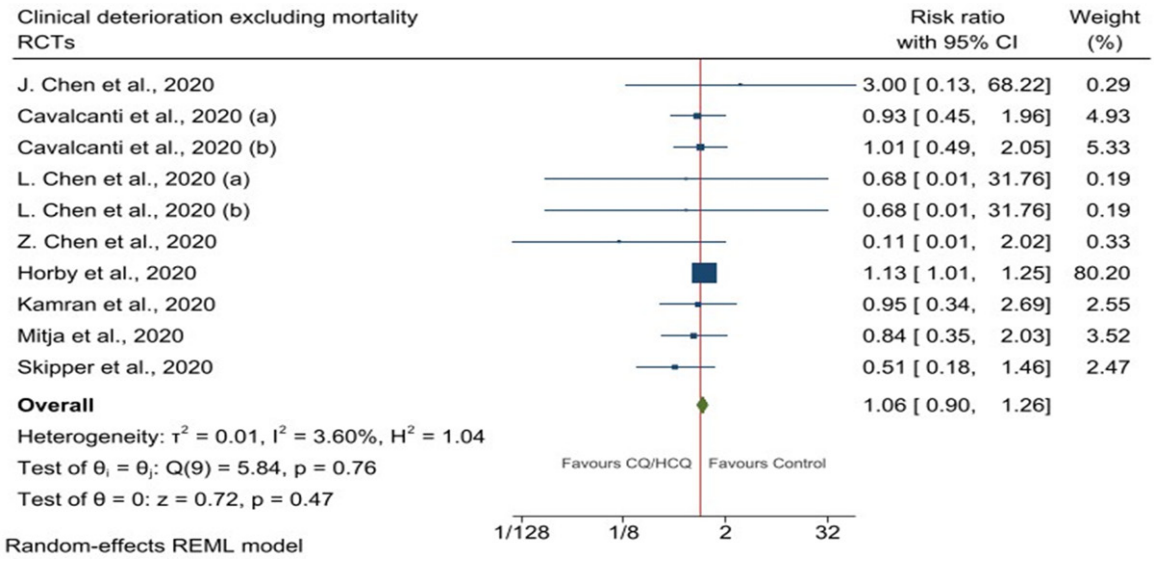
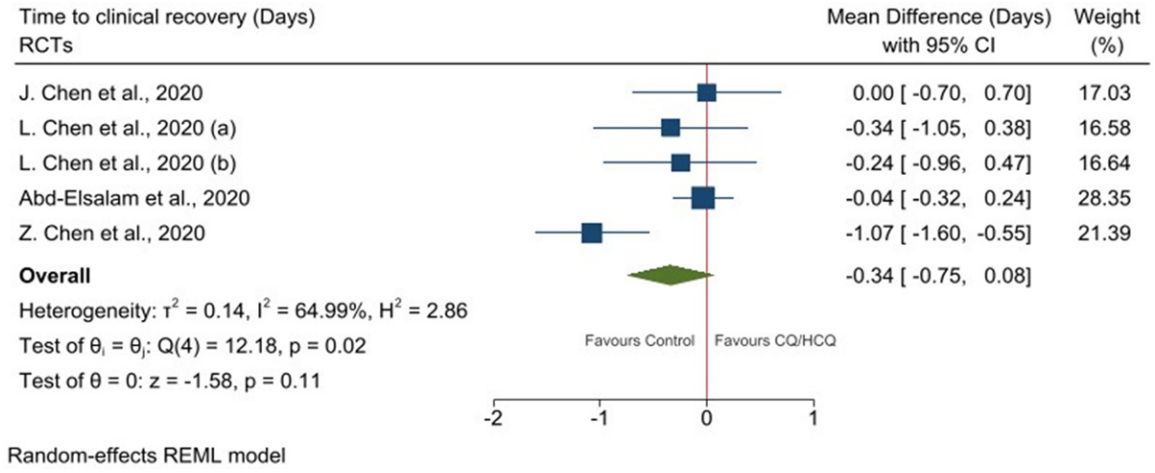
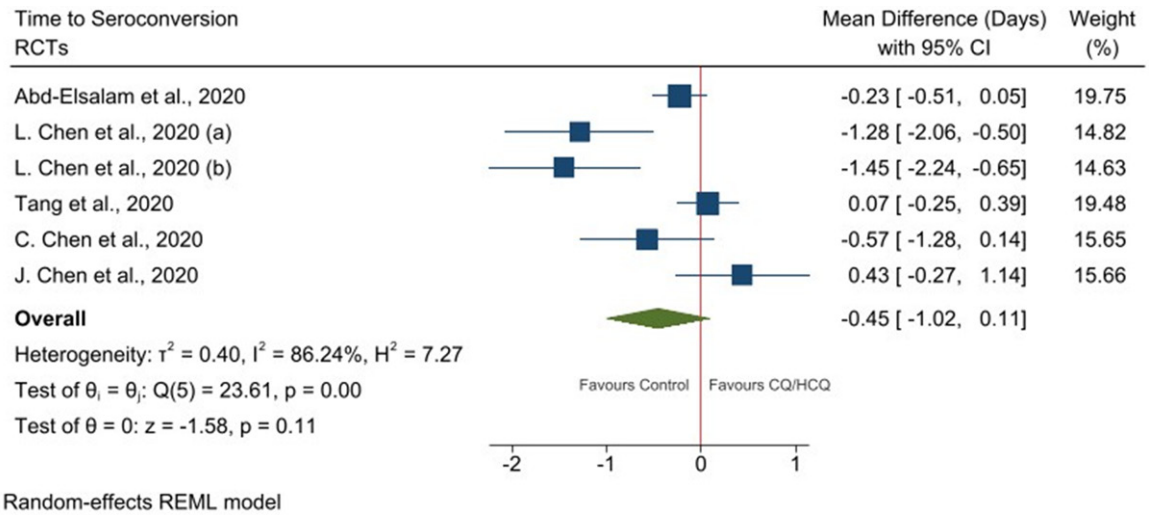


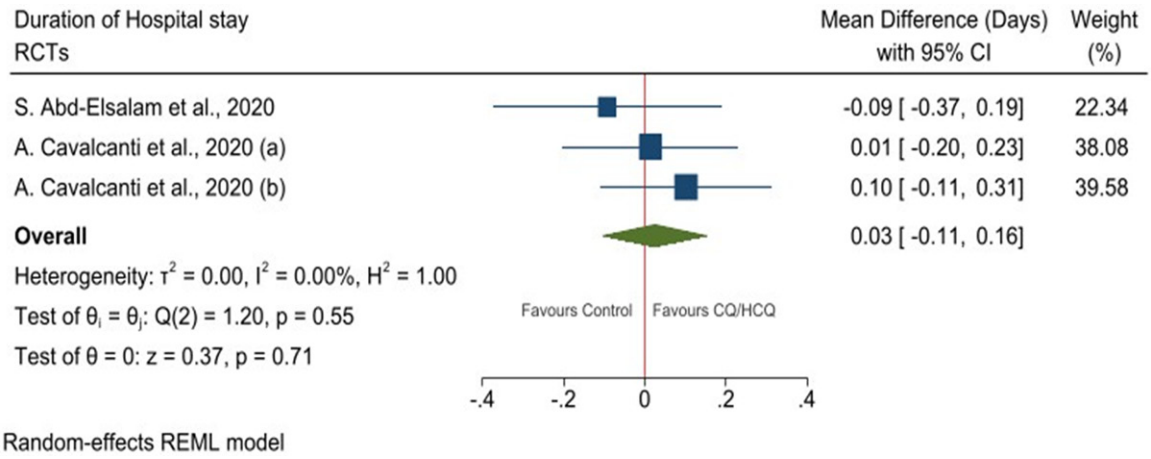
Supplementary Figure 1. Forest plot showing risk ratios for Clinical deterioration excluding mortality in patients randomized to CQ/HCQ vs Control (Usual care). Legend: L. Chen et al., 2020 (a) represents the trials arm CQ vs Control; L. Chen et al., 2020 (b) represents the trials arm HCQ vs Control; Cavalcanti et al., 2020 (a) represents the trials arm HCQ vs Control; Cavalcanti et al., 2020 (a) represents the trials arm HCQ+ZAM vs Control.



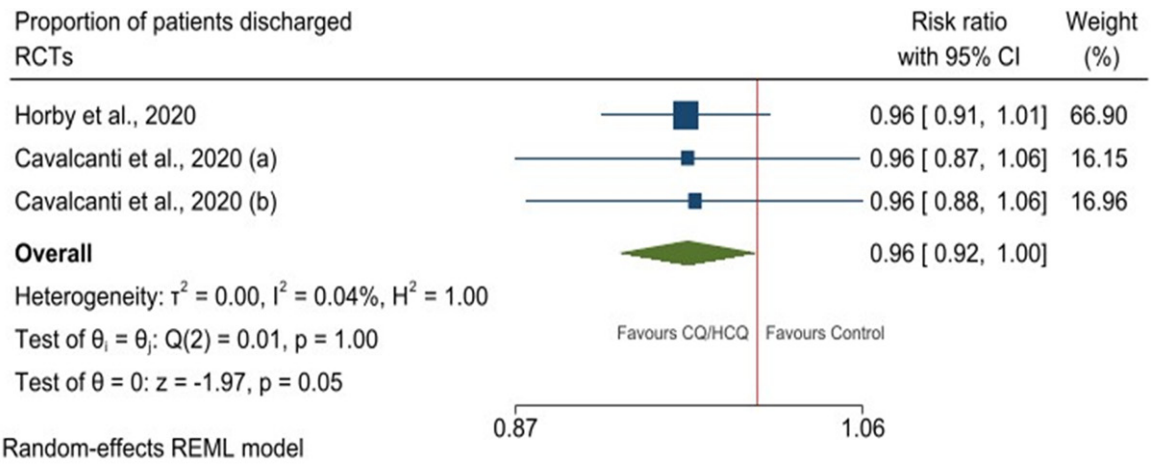
Supplementary Figure 2. Forest plot showing mean difference in time to clinical recovery in patients randomized to CQ/HCQ vs Control (Usual care). Legend: L. Chen et al., 2020 (a) represents the trials arm CQ vs Control; L. Chen et al., 2020 (b) represents the trials arm HCQ vs Control.



Supplementary Figure 3. Forest plot showing mean difference in time to seroconversion (negative PCR) in patients randomized to CQ/HCQ vs Control (Usual care). Legend: L. Chen et al., 2020 (a) represents the trials arm CQ vs Control; L. Chen et al., 2020 (b) represents the trials arm HCQ vs Control.



Supplementary Figure 4. Forest plot showing mean difference in duration of hospital stay in patients randomized to CQ/HCQ vs Control (Usual care). Legend: Cavalcanti et al., 2020 (a) represents the trials arm HCQ vs Control; Cavalcanti et al., 2020 (a) represents the trials arm HCQ+ZAM vs Control.



Supplementary Figure 5. Forest plot showing risk ratio for being discharged at the end of the study period in patients randomized to CQ/HCQ vs Control (Usual care). Legend: Cavalcanti et al., 2020 (a) represents the trials arm HCQ vs Control; Cavalcanti et al., 2020 (a) represents the trials arm HCQ+ZAM vs Control.