Hydroxychloroquine plus standard of care compared with standard of care alone in COVID-19: a meta-analysis of randomized controlled trials

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The efficacy and safety of Hydroxychloroquine (HCQ) in treating coronavirus disease (COVID-19) is disputed. This systematic review and meta-analysis aimed to examine the efficacy and safety of HCQ in addition to standard of care (SOC) in COVID-19. PubMed, the Cochrane Library, Embase, Web of sciences, and medRxiv were searched up to March 15, 2021. Clinical studies registry databases were also searched for identifying potential clinical trials. The references list of the key studies was reviewed to identify additional relevant resources. The quality of the included studies was evaluated using the Cochrane Collaboration tool and Jadad checklist. Meta-analysis was performed using RevMan software (version 5.3). Eleven randomized controlled trials with a total number of 8161 patients were identified as eligible for meta-analysis. No significant differences were observed between the two treatment groups in terms of negative rate of polymerase chain reaction (PCR) (Risk ratio [RR]: 0.99, 95% confidence interval (CI) 0.90, 1.08; P = 0.76), PCR negative conversion time (Mean difference [MD]: −1.06, 95% CI −3.10, 0.97; P = 0.30), all-cause mortality (RR: 1.09, 95% CI 1.00, 1.20; P = 0.06), body temperature recovery time (MD: −0.64, 95% CI −1.37, 0.10; P = 0.09), length of hospital stay (MD: −0.17, 95% CI −0.80, 0.46; P = 0.59), use of mechanical ventilation (RR: 1.12, 95% CI 0.95, 1.32; P = 0.19), and disease progression (RR = 0.82, 95% CI 0.37, 1.85; P = 0.64). However, there was a significant difference between two groups regarding adverse events (RR: 1.81, 95% CI 1.36, 2.42; P < 0.05). The findings suggest that the addition of HCQ to SOC has no benefit in the treatment of hospitalized patients with COVID-19. Additionally, it is associated with more adverse events.

The COVID-19 pandemic was identified and reported for the first time in Wuhan, China1–3, and has been recognized as a global public health concern by the World Health Organization (WHO)4. The mortality of critically ill patients with COVID-19 is considerable5. The initial estimations for the case fatality rate were about 2.3% in China6 and 7.2% in Italy7. The 2019-nCoV infection causes clusters of severe respiratory illnesses similar to severe acute respiratory syndrome (SARS) coronavirus and, in severe cases, is associated with hospitalization, ICU admission, and frequent mortalities8,9. Fever, coughing, shortness of breath, muscle ache, confusion, headache, sore throat, rhinorrhea, chest pain, diarrhea, nausea, and vomiting are among the clinical manifestations of the disease10. Early efforts have focused on describing the clinical course, containing severe cases, and treating the sick11.

There are several options for controlling and preventing the development of COVID-19 infections, including vaccines, monoclonal antibodies, oligonucleotide-based therapies, peptides, interferon therapies, and small-molecule drugs12. Lopinavir/Ritonavir (400/100 mg every 12 h), Chloroquine (500 mg every 12 h), and Hydroxychloroquine (HCQ) (200 mg every 12 h) and Alpha-interferon are also proposed as courses of treatment12. HCQ is used for a variety of diseases, including IgAN13,14, Arthritis15,16, Pulmonary Sarcoidosis17, Cutaneous lupus erythematosus18,19, Sjogren’s syndrome20, and Type 2 diabetes mellitus21. HCQ prevents the activity of lysosomal enzymes. This drug can reduce the production of cytokines, including type 1 interferons, and inhibit
T cell activation and the differentiation and expression of excitatory molecules (CD154)\textsuperscript{23}. Currently, several observational\textsuperscript{16,25} and clinical studies\textsuperscript{19,27} have evaluated the efficacy of HCQ on COVID-19. Besides, several meta-analyses examined HCQ in COVID-19 regarding a few of the outcomes, such as mortality and negative rate of polymerase chain reaction (PCR). Therefore, there is an urgent need to examine more detailed outcomes based on the available evidence. The purpose of this study was to examine whether HCQ in addition to standard of care (SOC) versus SOC alone is more effective and safer in hospitalized patients with COVID-19.

Methods

The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42020179425. When writing this report, we used the preferred reporting items for systematic reviews and meta-analysis (PRISMA)\textsuperscript{28}. The PRISMA statement consists of a 27-item checklist and a 4-phase flow diagram. We used the PRISMA checklist to prepare the report and diagram for the screening process.

Search strategy. A systematic review of the relevant literature was conducted in PubMed, The Cochrane Library, Embase, Web of Sciences, and medRxiv up to March 15, 2021. In order to increase the sensitivity of the search, Google Scholar was also searched. In addition, the European Union Clinical Trials Register, Clinical trial Gov. and Chinese Clinical Trial Registry (ChiCTR) were searched. Finally, the references list of the final studies and review articles were reviewed for more citations. The search terms used were 2019-nCoV, SARS-CoV-2, COVID-19, and Hydroxychloroquine, which were usually limited to the title and the abstract of the articles. We included articles with English full-text or abstract.

The following is our search strategy used to search for relevant articles published in PubMed: (((((COVID-19[Title/Abstract]) OR (SARS-CoV-2[Title/Abstract])) OR (Coronavirus[Title/Abstract])) OR (2019-nCoV[Title/Abstract])) OR (Novel coronavirus[Title/Abstract])) AND (Hydroxychloroquine[Title/Abstract]). We followed a similar logic while performing searches in other databases.

Study selection. Two researchers independently screened the identified studies based on the inclusion criteria. Disagreements were resolved by discussion among the authors. The following inclusion criteria were used for selecting the articles: (1) hospitalized patients with suspected or confirmed COVID-19 by laboratory tests; (2) HCQ plus SOC as intervention; (3) SOC alone as control; (4) randomized controlled trial as study design; (5) published as abstract or full-text; and (6) primary and secondary outcomes of interests (negative conversion time, negative rate of PCR, mortality rate, body temperature recovery time, length of hospital stay, and any adverse events). Other studies and reports such as letters to the editor, case reports, editorial comments, observational studies, and animal models were excluded.

Data extraction and quality assessment. The Cochrane risk of bias tool was used to assess the risk of bias in five domains (selection, performance, attrition, reporting, and other) in the included studies. We used the Jadad checklist to evaluate the quality of clinical trial studies. Information on the study characteristics (place, design, and duration); patient's characteristics (age, sex, and the number of patients); intervention and control (treatment protocol); efficacy outcomes; and adverse events were extracted. Both processes were independently performed by two authors, and disagreements were resolved by discussion among the authors.

Quantitative data synthesis. A meta-analysis was conducted to compare the efficacy and safety of HCQ plus SOC versus SOC alone using the RevMan (version 5.3) software which is recommended by the Cochrane Handbook for Systematic Reviews of Interventions. The mean difference (MD) and risk ratio (RR) with a 95% confidence interval (CI) were used for continuous and dichotomous variables, respectively. Statistical heterogeneity was evaluated using I-square > 50% and Chi-square with a significance level p < 0.1. The random-effects method was used for statistical heterogeneity; otherwise, the fixed-effect method was used.

Results

Study characteristics. Figure 1 shows the process of literature search, removal of duplication, and screening. Of the total 1,205 records, 1,098 were excluded based on the title and abstract. The remaining 107 records were review for full text. Finally, eleven randomized controlled trials (RCTs)\textsuperscript{26,29-38} with 8161 patients were included in the meta-analysis. The main characteristics of the selected studies are presented in Table 1. Assessment of the risk of bias using the Cochrane Collaboration tool is presented in Fig. 2.

Outcomes. Primary outcomes. The meta-analysis demonstrated that there was no significant difference between the HCQ plus SOC group and SOC group in terms of the negative rate of PCR (RR: 0.99, 95% CI 0.90, 1.08; P = 0.76), PCR negative conversion time (MD: − 1.06, 95% CI − 3.10, 0.97; P = 0.30), and all-cause mortality (RR: 1.13, 95% CI 0.99 1.27, P = 0.06) (Fig. 3).

Secondary outcomes. The pooled RR of included studies showed that adding HCQ to SOC was not associated with significant effect on secondary outcomes including body temperature recovery time (MD: − 0.64, 95% CI − 1.37, 0.10; P = 0.09), the length of hospital stay (MD: − 0.17, 95% CI − 0.80 0.46, P = 0.59), the use of mechanical ventilation (RR: 1.12, 95% CI 0.95, 1.32; P = 0.19), and disease progression (RR: 0.82, 95% CI 0.37, 1.85; P = 0.64) (Fig. 3). The pooled RR of 5 studies showed that the addition of HCQ to SOC was associated with higher rates of adverse events in hospitalized patients (RR: 1.81, 95% CI 1.36, 2.42; P < 0.05) (Fig. 4). However,
there was no significant difference between the two groups in terms of serious adverse events (RR: 1.29, 95% CI 0.50, 3.30; P = 0.60) (Fig. 4).

**Sensitivity analysis and subgroup analysis.** The findings of the subgroup analysis are presented in Table 2. The findings showed that primary outcomes did not change regarding dose, sample size, treatment duration, and severity of COVID-19. We performed a sensitivity analysis based on different settings and control groups. For this reason, we included RCTs done on non-hospitalized patients and RCTs with placebo as control. The result did not change in terms of the negative rate of PCR and mortality rate (Table 2).

**Discussion**

The purpose of this study was to examine the efficacy and safety of HCQ plus SOC compared to SOC alone for COVID-19.

Several RCTs have examined the efficacy and safety of HCQ in treating COVID-19. The findings of our meta-analysis showed that the addition of HCQ to SOC in patients with COVID-19 was not associated with significant improvement in any outcomes reported in patients. Previously published meta-analyses on observational studies and RCTs also found no clinical benefits for HCQ in comparison with SOC for COVID-19 patients, which confirms our findings. Gautret et al. suggested that the causes of insufficient response to treatment with HCQ in the non-respondents with COVID-19 should be examined by factors such as SARS-CoV-2 strains, genome, and other associated factors with the metabolism of HCQ in patients. A possible mechanism for HCQ inefficiency was explained by Sandeep and McGregor using virtualized quantum mechanical modeling. However, Yao et al. found that HCQ was more potent than Chloroquine in inhabiting SARS-CoV-2 in vitro.

It should be noted that most of the included studies in these meta-analyses were observational. There are some concerns regarding the limitations of these studies that should be considered. All kinds of biases such as confounding, reverse causation, statistical considerations, and other issues are limitations of these studies in the estimation of drug efficacy and safety. The Agency for Healthcare Research and Quality (AHRQ) has provided recommendations on including observational studies in the comparative effectiveness review process for
| Author, year | Place    | Patients (N, male) | Age  | Diagnosis | Intervention (N, HCQ protocol) | SOC (N, protocol) | Jadad scale |
|-------------|----------|--------------------|------|-----------|-------------------------------|-----------------|-------------|
| Abd-Elsalam, 2020 | Egypt    | 194,118            | 40.72| PCR       | 97; 400 mg twice/day (in day 1) followed by 200 mg tablets twice/day + SOC | 97; Paracetamol, oxygen, fluids, empicic antibiotic, oseltamivir, and invasive mechanical ventilation | 3           |
| Chen Z, 2020   | China    | 62, 29             | 44.7 | RT-PCR    | 31; (400 mg/day (200 mg/bid) between days 1 and 5) + SOC | 31; Oxygen therapy, antiviral and antibacterial agents, immunoglobulin, corticosteroids | 2           |
| Chen J, 2020   | China    | 30, 21             | 48.6 | PCR       | 15; (400 mg per day for 5 days) + SOC | 15; O2 therapy, interferon, lopinavir/ritonavir, antibodies, and supportive treatment | 2           |
| Chen CP, 2020  | Taiwan   | 33, 19             | 32.9 | RT-PCR    | 21; HCQ 400 mg twice for 1 day and HCQ 200 mg twice daily for 6 days + SOC | 12; Ceftriaxone, azithromycin, levofloxacin, moxifloxacin, Oseltamivir | 2           |
| Chen L, 2020   | China    | 66, 15             | NR   | RT-PCR or CT | 18; 200 mg Bid for 10 days | 12; NR | 3           |
| Cavalcanti, 2020 | Brazil   | 504, 265           | 50.3 | NR        | 221; HCQ 400 mg twice daily, for 7 days + SOC | 227; Glucocorticoids, immunomodulators, antibiotic and antiviral agents | 4           |
| Kamran, 2020   | Pakistan | 500,466            | 35.96| PCR       | 349; HCQ 400 mg twice a day for day one followed by 200 mg 12 hourly for next 3 days + SOC | 151; Vit C, zinc, Vit-D, Paracetamol, intravenous fluids, hemodynamic monitoring parameters | 3           |
| Lyngbakken, 2020 | Norway   | 53, 35             | 62   | RT-PCR    | 27; HCQ 400 mg twice for 7 days + SOC | 26; NR | 2           |
| RC Group, 2020 | UK       | 4716, 2935         | NR   | NR        | 1561; 800 mg at 0 and 6 h; 400 mg at 12 h; 400 mg × 9 days + SOC | 3155; NR | 2           |
| Tang, 2020     | China    | 150, 82            | 46   | Real time RT-PCR | 75; HCQ 1200 mg/day × 3 day followed by 800 mg/day + SOC | 75; Intravenous fluids, supplemental oxygen, hemodynamic monitoring, and intensive care | 3           |
| WHO Solidarity Trial, 2021 | 30 Countries | 1853,1109        | NR   | NR        | 947,800 mg at 0 and hour 6, starting at hour 12, 800 mg for 10 days | 906; NR | 2           |

Table 1. The characteristics of RCTs included in the meta-analysis. CT: Computed tomography, HCQ: Hydroxychloroquine, NR: Not reported, PCR: Polymerase chain reaction, RT-PCR: Reverse transcription polymerase chain reaction.

Our meta-analysis showed that HCQ was not associated with a significant reduction or increase in the COVID-19 mortality rate. The results from similar meta-analyses are in line with our findings. Moreover, we conducted a sensitivity analysis of studies done in nonhospital patients and placebo as a control, plus included RCTs regarding the negative rate of PCR and mortality rate. The result did not show any significant differences. Fiolet et al. also found that HCQ was not associated with a different mortality rate in all studies and RCTs, which confirms our findings.

Some studies have supported the synergistic effect of HCQ with Azithromycin on COVID-19. In an open-label non-randomized clinical trial, Gautret et al. found that 100% of patients who received HCQ and Azithromycin as combination therapy successfully recovered from COVID-19. These authors found similar results in another study. A meta-analysis showed that HCQ alone or in combination with Azithromycin in comparison with the control group was not effective in treating COVID-19 and was associated with higher mortality rates. It seems that there is no benefit for HCQ in combination with Azithromycin, and it is associated with an increased risk of bacterial resistance (2.7-fold).

Our meta-analysis showed that as an add-on therapy to SOC was associated with more adverse events. Reported adverse events in RCTs were mainly mild. Three RCTs reported serious adverse events in patients taking HCQ and SOC. However, this difference was not statistically significant. Generally, adverse effects of antimalarial are usually rare and mild. Gastric symptoms are a prevalent adverse effect of HCQ; other adverse events include Cutaneous, headache, Cardiomyopathy, and Retinopathy. Regarding the short-term follow-up of the studies, it is recommended that patients who received HCQ should be monitored for possible adverse events over a longer period of time.

Limitations. High heterogeneity between studies, the use of different treatment protocols as SOC, short follow-up periods, and lack of rigorous methodologies of the studies were among the limitations of our study. Nevertheless, the findings of this study can be beneficial for guiding clinicians in decisions regarding COVID-19 treatment.
Conclusion
According to the findings of this study, HCQ in addition to SOC appears to be not an effective treatment in primary outcomes, including negative conversion time, the negative rate of PCR, and mortality rate. In addition, HCQ did not show a significant improvement in other secondary outcomes. HCQ was also associated with higher rates of adverse events.
Figure 3. Forest plot of HCQ plus SOC vs. SOC for primary outcomes; Negative conversion time (A), Negative rate of PCR (B), and All-cause mortality (C) in COVID-19 patients.
Figure 4. Forest plot of HCQ plus SOC vs. SOC for primary outcomes; Body temperature recovery time (A), Mechanical ventilation (B), Hospital stay (C), Disease progression (D), Any adverse event (E), and Serious adverse events (F) in COVID-19 patients.
### Table 2. Sensitivity analysis and subgroup analysis for primary outcomes.

| Analysis                              | No. of studies | MD or RR (95% CI)       | P     | Heterogeneity |
|---------------------------------------|----------------|-------------------------|-------|---------------|
|                                       |                |                         |       |               |
| **Sensitivity analysis**               |                |                         |       |               |
| Negative rate of PCR                  | 5              | 0.96 [0.87, 1.06]       | 0.45  | 0.93          | 0.92 | 0%    |
| Mortality                             | 9              | 1.07 [0.98, 1.17]       | 0.13  | 3.45          | 0.90 | 0%    |
| **Subgroup analysis**                 |                |                         |       |               |
| PCR Negative conversion time          |                |                         |       |               |
| Dose                                  | 4              |                         |       |               |
| 400 mg/day*                           | 2              | −1.07 [−7.57, 5.43]     | 0.75  | 58.80         | <0.05| 98%   |
| >400 mg/day on first day*             | 2              | −2.11 [−4.54, 0.33]     | 0.09  | 6.39          | 0.01 | 84%   |
| **Treatment duration with HCQ**       |                |                         |       |               |
| <7 days                               | 2              | 0.23 [−1.37, 1.82]      | 0.84  | 26.44         | <0.05| 96%   |
| ≥7 days                               | 3              | −1.41 [−4.08, 1.27]     | 0.34  | 104.30        | <0.05| 98%   |
| **Sample size**                       |                |                         |       |               |
| <100                                  | 5              |                         |       |               |
|                                        |                | −1.87 [−6.30, 2.57]     | 0.41  | 63.26         | <0.05| 97%   |
| ≥100                                  | 2              | 0.03 [−1.93, 1.99]      | 0.98  | 27.30         | <0.05| 96%   |
| **Severe of COVID-19**                |                |                         |       |               |
| Mild/moderate                         | 3              | 0.07 [−2.21, 2.34]      | 0.96  | 27.87         | <0.05| 93%   |
| Moderate                              | 5              |                         |       |               |
|                                        | 1              | −4.38 [−5.52, −3.24]    | <0.05 | −           | −     | −     |
| Mild/moderate/severe                  | 1              | −1.00 [−1.72, −0.28]    | <0.05 | −           | −     | −     |
| **Negative rate of PCR**              |                |                         |       |               |
| At two time points                     |                |                         |       |               |
| On day 7                              | 3              | 1.02 [0.69, 1.52]       | 0.91  | 13.73         | 0.001| 85%   |
| On day 14                             | 3              | 0.97 [0.89, 1.07]       | 0.58  | 0.35          | 0.84 | 0%    |
| **Sample size**                       |                |                         |       |               |
| <100                                  | 4              |                         |       |               |
|                                        | 2              | 1.00 [0.80, 1.24]       | 0.97  | 0.50          | 0.48 | 0%    |
| ≥100                                  | 2              | 0.97 [0.87, 1.08]       | 0.58  | 0.08          | 0.92 | 0%    |
| **Severe of COVID-19**                |                |                         |       |               |
| Mild/moderate                         | 4              |                         |       |               |
|                                        | 1              | 1.00 [0.80, 1.24]       | 0.97  | 0.50          | 0.48 | 0%    |
| Mild                                  | 1              | 0.96 [0.85, 1.08]       | 0.05  | −            | −     | −     |

*Patients were given a fixed-dose 400 mg/day during treatment. *Patients were given a dose higher than 400 mg on the first day, then a fixed dose of 400 mg/day for other days.

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Ba.A. and Be.A. systematically reviewed the search results and selected the relevant studies. Ba.A. performed the formal analysis. All authors performed the literature search, wrote the manuscript, and reviewed the manuscript.

Competing interests
The authors declare no competing interests.

Additional information

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