

# INPLASY PROTOCOL

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## Chloroquine and hydroxychloroquine for treatment of COVID-19: a systematic review and meta-analysis

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**Conflicts of interest:**  
We declare no conflicts of interests.

**Review question / Objective:** Absence of an effective treatment made it difficult for clinicians to respond effectively against the global pandemic caused by coronavirus disease 2019 (COVID-19). Chloroquine (CQ) and hydroxychloroquine (HCQ) had shown potential therapeutic value for COVID-19. However, there is a clear controversy of their efficacy and safety in patients. We reassessed the safety and efficacy characteristics of CQ and HCQ based on a comprehensive analysis of current reports on their use in the treatment of COVID-19. The aim of our study was to provide a new strategy for the clinical application of CQ and HCQ and to advice on the development of new drugs. For this systematic review and meta-analysis, we searched PubMed, Web of Science, Wan Fang Chinese database and Zhi Wang Chinese database to find appropriate studies in June 2020. Research articles including observational studies and clinical trials were included, the outcomes of efficacy and safety in CQ or HCQ group with their control group were extracted from these published studies. Reviews, case reports, studies with insufficient data or non-randomized trials were excluded. Odds ratios(OR) with 95% CI were used to evaluate relative outcomes and heterogeneity were all well explained. Subgroup analysis, single-arm meta-analysis and cumulative meta-analysis were also conducted.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 July 2020 and was last updated on 25 July 2020 (registration number INPLASY202070110).

### INTRODUCTION

**Review question / Objective:** Absence of an effective treatment made it difficult for

clinicians to respond effectively against the global pandemic caused by coronavirus disease 2019 (COVID-19). Chloroquine (CQ) and hydroxychloroquine (HCQ) had shown

potential therapeutic value for COVID-19. However, there is a clear controversy of their efficacy and safety in patients. We reassessed the safety and efficacy characteristics of CQ and HCQ based on a comprehensive analysis of current reports on their use in the treatment of COVID-19. The aim of our study was to provide a new strategy for the clinical application of CQ and HCQ and to advice on the development of new drugs. For this systematic review and meta-analysis, we searched PubMed, Web of Science, Wan Fang Chinese database and Zhi Wang Chinese database to find appropriate studies in June 2020. Research articles including observational studies and clinical trials were included, the outcomes of efficacy and safety in CQ or HCQ group with their control group were extracted from these published studies. Reviews, case reports, studies with insufficient data or non-randomized trials were excluded. Odds ratios(OR) with 95% CI were used to evaluate relative outcomes and heterogeneity were all well explained. Subgroup analysis, single-arm meta-analysis and cumulative meta-analysis were also conducted.

**Condition being studied:** Chloroquine (CQ) and hydroxychloroquine (HCQ) are used for the treatment of autoimmune diseases and rheumatoid arthritis, but at the same time, their anti-inflammatory and broad-spectrum antiviral effects, especially anti-coronavirus activity, had aroused people's high attention. The potential curative effects of chloroquine were also reported for SARS-CoV and MERS-CoV which similar to COVID-19. Thus, CQ and HCQ have been suggested as effective treatments for COVID-19 and probably were the first molecules to be used in most countries in the world for the infected patients. Fortunately, the antiviral properties of CQ and HCQ brought a lot of expectations according to their in vitro experiments and they were included in the COVID-19 treatment guidelines all over the world. However, there is a clear controversy for their efficacy and safety in patients. There are some consensuses about the research of HCQ and CQ, but there are also contradictions. Trials are

now registered weekly at Clinicaltrail.gov, therefore, it is urgent to summarize the early results to better guide the next clinical study, and to buy time and resources for the treatment of COVID-19, that is also the purpose of our meta-analysis.

## METHODS

**Search strategy:** Our systematic review and meta-analysis focus on the effects of chloroquine or hydroxychloroquine on virus clearing, outcomes and safety in persons infected with SARS-CoV-2. We searched PubMed, Web of Science, Chinese database Wan Fang, and Zhi Wang from inception using the terms: "coronavirus," OR "COVID-19," OR "2019-nCoV," OR "SARS-CoV-2" OR "severe acute respiratory syndrome," AND "chloroquine" OR "hydroxychloroquine," with these Boolean operators.

**Participant or population:** Patients treated with CQ/HCQ/HCQ combined with other drugs comparing with treated with none of these drugs.

**Intervention:** Patients treated with CQ/HCQ/HCQ combined with other drugs.

**Comparator:** Patients treated with none of these drugs.

**Study designs to be included:** RCT and cohort.

**Eligibility criteria:** Studies met our inclusion criteria were those research articles including observational studies and clinical trials on the use of chloroquine or hydroxychloroquine in persons with SARS-CoV-2 infections. Meanwhile, included studies should contain relevant data on virus clearance and/or death, outcomes and adverse events after treatment of CQ and HCQ. Virus clearing efficacy should include nucleic acid testing after treatment, or improvement in symptoms or survival. We will choose article published both in Chinese and English as long as it meets our inclusion criteria.

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**Information sources:** PubMed, Web of Science, Chinese database Wan Fang, and Zhi Wang.

**Main outcome(s):** Main outcome contains negative or positive rate and mortality of patients infected with SARS-CoV-2 after chloroquine or hydroxychloroquine treatment and improvement in the patients' condition after treatment.

**Additional outcome(s):** Secondary outcome was adverse events and drug combination effects in CQ and HCQ treatment.

**Quality assessment / Risk of bias analysis:** The Cochrane risk of bias tool was used for evaluating the risk of bias for each of the included publications<sup>16</sup>. We provided a standard of 'low risk', 'high risk' or 'unclear risk' of bias according to the following entries: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, validity of outcome measure, and baseline comparability/imbalance for age and gender. The studies having a low risk of bias were judged if they had a low risk of bias for all of these above entries.

**Strategy of data synthesis:** Negative rate of patients who infected with SARS-CoV-2 after chloroquine or hydroxychloroquine treatment and improvement in the patients' condition after treatment were considered as successful virus clearing and included in the analysis for drug efficacy. Mortality of patients was included in the analysis for mortality. All the incidence of adverse events were included in the analysis for safety.

**Subgroup analysis:** We divided the studies of HCQ treatment into 2 subgroups according to the days of drug accumulation before evaluating the efficacy of hydroxychloroquine. We divided the studies into 3 subgroups, depending on when patients were assessed for mortality.

**Sensitivity analysis:** The heterogeneity test was conducted using Cochran Chi-square

test and I<sup>2</sup>. There was no obvious heterogeneity when  $P \geq 0.05$  or  $I^2 < 50\%$  and a fixed-effects model was used. The random-effects model was used when the obvious heterogeneity appeared. To address the heterogeneity, subgroup analysis and sensitivity analysis were performed.

**Language:** English.

**Country(ies) involved:** China.

**Keywords:** COVID-19, hydroxychloroquine, chloroquine.

**Dissemination plans:** Publish in a journal.

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