Systematic Review

Hydroxychloroquine and chloroquine for COVID-19 infection. Rapid systematic review

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ABSTRACT | CONTEXT: Based on the results of preliminary studies, the off-label use of hydroxychloroquine for COVID-19 infection has been observed in practice. **OBJECTIVES:** To identify, systematically assess and summarize the best available evidence on the efficacy and safety of the use of hydroxychloroquine and chloroquine for COVID-19 infection. **METHODS:** Rapid systematic review. **RESULTS:** After the selection process, 30 studies were included: one open-label randomized trial, one open-label non-randomized trial and 28 ongoing studies. The outcome 'detection of viral load in oral swab' (surrogate outcome) was evaluated by both studies, involving a total of 72 participants. The findings of the studies were discordant: one study observed a higher frequency of negative viral load associated with hydroxychloroquine on day-7, while the other study did not observe any difference between hydroxychloroquine and the control group (standard treatment) on day-6. Both studies have methodological limitations when evaluated by specific tools according to study design (Cochrane Bias Risk Table and ROBINS-I). **CONCLUSION:** This rapid systematic review identified two clinical studies (with available data), with limited methodological quality, that evaluated the effects of hydroxychloroquine for COVID-19 infection. Based on the findings of these two studies, the efficacy and safety of hydroxychloroquine and chloroquine in patients with COVID-19 is still uncertain (very low evidence certainty) and its routine use for this situation should not be recommended until the results of ongoing studies could provide a proper assessment of their effects.

KEYWORDS: COVID-19. SARS-CoV-2. Coronavirus. Hydroxychloroquine. Chloroquine. Systematic review

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Introduction

Since December 2019, when the first outbreak of COVID-19 infection was revealed in China (Wuhan, Hubei province), researches have been conducted to discover rapid and accurate diagnosis tests, to develop vaccines and to assess therapeutic options for the treatment and prevention of this disease and its complications, as SARS-Cov-2.

Funding agencies are prioritizing resources for several studies that aim to elucidate the epidemiological features, pathophysiology, risk factors, prognosis and clinical evolution of the emerging virus.

The COVID-19 pandemics has mobilized research organizations, database, renowned publishers and editorial groups - as examples the Royal Society of Tropical Medicine and Hygiene, Elsevier, Cochrane, University of Oxford and British Medical Journal - which have been currently working to provide open access scientific content of COVID-19 for healthcare professionals and general population.

In front of a pandemic, all those actions are expected and must be recognized as legitimates attempts to minimize the consequences of a new disease that seems to be highly transmissible and associated with major complications, elevated number of admissions on intensive care units, high costs and resources consumption, and an unpredictable economic impact worldwide.

However, the expectation that 'new discoveries' can substantially change this uncertain scenario should be based on reliable and objective data. The expectation should not ignore or underestimate the methodological rigor of the available researchers, and it's necessary to differentiate the obvious from the evidence and the pathophysiological rationale from the results of a well-planned and -conducted clinical trial.

Based on preliminary data, healthcare authorities have recommended the use of hydroxychloroquine or chloroquine for treating COVID-19[1-3].

The scarcity of these drugs for those patients with diseases for which they are formally indicated - including chronic autoimmune diseases such as lupus erythematosus and rheumatoid arthritis - is already a reality.

In order to scientifically and impartially inform health decision making, a rapid systematic review was developed to map and critically assess the best existing evidence on the use of hydroxychloroquine and chloroquine for COVID-19 infection.

Objectives

To identify, systematically appraise and summarize the available scientific evidence on the efficacy and safety of the use of hydroxychloroquine and chloroquine for COVID-19 infection.

Structured research question (PICO acronym):

- P (population): people with suspect or confirmed COVID-19 infection.
- I (intervention): hydroxychloroquine or chloroquine (isolated or combined with other interventions).
- C (comparators): general health support care, placebo, no specific intervention or any other active treatment.
- O (outcomes): efficacy and safety outcomes detailed under the methods section.
- S (studies): clinical studies or secondary studies that considered clinical studies as an inclusion criteria.

Methods

Study design and setting

This was a rapid systematic review developed at Center of Health Technology Assessment, Hospital Sírio-Libanês in collaboration with the Discipline of Economics and Health Management, Universidade Federal de São Paulo (Unifesp), São Paulo - Brazil. This review was conducted in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[4]. This manuscript was written following the PRISMA Statement[5]. Since this was a rapid systematic review, a register on the PROSPERO database has not been consolidated.

Eligibility criteria

(a) Types of participant types
Adults and children with suspected or confirmed diagnosis of COVID-19 infection.
(b) Types of interventions
Hydroxychloroquine or chloroquine alone or in combination with other interventions.
(c) Types of studies

Taking into account the limited number of studies that may have been published so far and that the purpose of this review is to map the current knowledge, the following study designs were considered, following the hierarchy of evidence and considering their methodological quality: randomized clinical trials, quasi-randomized clinical trials, non-randomized clinical trials, cohort studies, case-control studies, single-arm experimental cohort studies (phase 1 or 2).

Outcomes of interest

We consider any clinical and laboratory outcomes as reported by the included studies, prioritizing the following:

Primary outcomes

- Mortality related to COVID-19.
- Severe adverse events.
- Progression to COVID-19 acute respiratory syndrome (SARS-Cov-2).

Secondary outcomes

- All-cause mortality
- Admission to an intensive care unit
- Any adverse event
- Health-related quality of life

Tertiary outcomes

- Laboratory outcomes

Searching for studies

Electronic search

An electronic search was performed in the following general databases:

- Cochrane Library (via Wiley);
- Embase (via Elsevier);
- Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS, via Biblioteca Virtual em Saúde, BVS)
- Medical Literature Analysis and Retrieval System Online (MEDLINE, via PubMed).

An electronic search was performed on the following grey literature database:

- Opengrey (https://opengrey.eu)

An electronic search was performed in the following clinical trial registry databases:

- ClinicalTrials.gov (https://clinicaltrials.gov)
- International Clinical Trials Register Platform (ICTRP), World Health Organization (WHO), which includes among other the Chinese Clinical Trial Registry (https://www.chictr.org.cn).

The search strategies developed and ran for each electronic database are presented in Chart 1. No restrictions on date, language or status (abstract or full text) of the publication were imposed. The searches were carried out on March 19th and updated on March 26th, 2020 (with the exception of ICTRP which was temporarily inactive).

Chart 1. Search strategies for electronic databases and other sources (to be continued)

Database	Search strategy	Results
Cochrane Library	#1 MeSH descriptor: [Coronavirus] explode all trees #2 "COVID-19" OR (COVID) OR (Coronavirus) OR (SARS-CoV-2) OR (Coronaviruses) OR (Deltacoronavirus) OR (Deltacoronaviruses) OR "Munia coronavirus HKU13" OR (Coronavirus HKU15) OR (Coronavirus, Rabbit) OR (Rabbit Coronavirus) OR (Coronaviruses, Rabbit) OR (Rabbit Coronaviruses) OR "Bulbul coronavirus HKU11" OR "Thrush coronavirus HKU12" #3 #1 OR #2 #4 MeSH descriptor: [Hydroxychloroquine] explode all trees #5 MeSH descriptor: [Hydroxychloroquine] explode all trees #6 MeSH descriptor: [Antimalarials] explode all trees #7 (Hydroxychloroquine) OR (Oxychlorochin) OR (Oxychloroquine) OR (Hydroxychlorochin) OR (Plaquenil) OR (Hydroxychloroquine Sulfate) OR "Hydroxychloroquine Sulfate (1:1) Salt" OR (Hidroxicloroquina) OR (Hydroxychloroquine) OR (Hydroxychloroquinum) OR (Oxichlorochine) OR (Oxichloroquine) OR Chlorochin OR Cloroquina OR Cloroquine OR Chloroquine OR (Antimalarials) OR (Antimalarial Agents) OR (Agents, Antimalarial) OR (Antimalarial Drugs) OR (Drugs, Antimalarial) OR (Anti-Malarials) OR (Anti Malarials) OR "(N4-(7-Chloro-4-quinolinyl)-N1,N1-diethyl-1,4-pentanediamine)" OR Hydroquin OR Axemal OR Dolquine OR Quensyl OR Quinoric OR Plaquenil #8 #4 OR #5 OR #6 OR #7 #9 #3 AND #8	2
Embase	#1 'coronavirinae' OR 'coronavirinae'/exp OR coronavirinae OR 'corona virus'/exp OR 'corona virus' OR 'coronavirus'/exp OR coronavirus OR 'covid-19' OR covid OR 'sars-cov-2' OR coronaviruses OR deltacoronavirus OR deltacoronaviruses OR 'munia coronavirus hku13' OR 'coronavirus hku15' OR 'coronavirus, rabbit' OR 'rabbit coronavirus' OR 'coronaviruses, rabbit' OR 'rabbit coronaviruses' OR 'bulbul coronavirus hku11' OR 'thrush coronavirus hku12'	24

Chart 1. Search strategies for electronic databases and other sources (continuation)

	#2 'hydroxychloroquine' OR 'hydroxychloroquine'/exp OR hydroxychloroquine OR '7 chloro 4 [4 [ethyl (2 hydroxyethyl) amino] 1 methylbutylamino] quinoline'/exp OR '7 chloro 4 [4 [ethyl (2 hydroxyethyl) amino] 1 methylbutylamino] quinoline' OR '7 chloro 4 [4 [ethyl (2 hydroxyethyl) amino] 1 methylbutylamino] quinoline diphosphate'/exp OR '7 chloro 4 [4 [ethyl (2 hydroxyethyl) amino] 1 methylbutylamino] quinoline diphosphate' OR 'chloroquinol'/exp OR chloroquinol OR 'ercoquin'/exp OR ercoquin OR 'hydrochloroquine'/exp OR hydrochloroquine OR 'hydrocloroquine'/exp OR hydrocloroquine OR 'oxychloroquine'/exp OR oxychloroquine OR 'quensyl'/exp OR quensyl OR 'sn 8137'/exp OR 'sn 8137' OR oxychlorochin OR hydroxychlorochin OR plaquenil OR 'hydroxychloroquine sulfate' OR 'hydroxychloroquine sulfate (1:1) salt' OR hidroxicloroquina OR hydroxychloroquinum OR oxichlorochine OR oxichloroquine OR 'chloroquine' OR 'chloroquine'/exp OR chloroquine OR '4 (4 diethylamino 1 methylbutylamino) 7 chlorchinolin diphosphate' OR '4 (4 diethylamino 1 methylbutylamino) 7 chlorchinolin sulfate' OR '4 (4 diethylamino 1 methylbutylamino) 7 chlorchinolin sulfate' OR '4 (4 diethylamino 1 methylbutylamino) 7 chloroquinoline' OR '7 chloro 4 (4 diethylamino 1 methylbutylamino) quinoline' OR '7 chloro 4 (4 diethylamino 1 methylbutylamino) quinoline diphosphate' OR '7 chloro 4 (4 diethylamino 1 methylbutylamino) quinoline' OR 'a-cq' OR amokin OR amokine OR anoclor OR aralan OR aralen OR 'aralen hydrochloride' OR 'aralen phosphate' OR aralene OR arechin OR arechine OR arequine OR arthrochin OR arthrochine OR arthroquine OR artrichin OR artrichine OR artriquine OR avloclor OR avoclor OR bemaphata OR bemaphate OR bemasulph OR bipiquin OR cadiquin OR chemochin OR chemochine OR chingamine OR chingaminum OR chloraquine OR chlorochin OR chlorochine OR chlorofoz OR chloroquin OR 'chloroquin phosphate' OR 'chloroquine diphosphate' OR 'chloroquine disulfate' OR 'chloroquine disulphate' OR 'chloroquine hydrochloride' OR 'chloroquine phosphate' OR 'chloroquine streuli' OR 'chloroquine sulfate' OR 'chloroquine sulphate' OR chloroquinesulphate OR 'chloroquini diphosphas' OR 'chloroquinum diphosphoricum' OR chlorquin OR chlorquine OR choloquine OR 'choroquine sulfate' OR 'choroquine sulphate' OR cidanchin OR 'clo-kit junior' OR clorichina OR clorichine OR cloriquine OR clorochina OR delagil OR delagyl OR dichinalex OR diclokin OR diquinalex OR diroquine OR emquin OR genocin OR gontochin OR gontochine OR gontoquine OR heliopar OR imagon OR iroquine OR klorokin OR klorokine OR klorokinfosfat OR lagaquin OR malaquin OR malarex OR malarivon OR malaviron OR maliaquine OR maquine OR mesylith OR mexaquin OR mirquin OR nivachine OR nivaquin OR nivaquine OR 'nivaquine (b)' OR 'nivaquine b' OR 'nivaquine dp' OR 'nivaquine forte' OR 'p roquine' OR quinachlor OR quingamine OR repal OR resochen OR resochene OR resochin OR 'resochin junior' OR resochina OR resochine OR resochinon OR resoquina OR resoquine OR reumachlor OR roquine OR 'rp 3377' OR rp3377 OR sanoquin OR sanoquine OR silbesan OR siragan OR sirajan OR 'sn 7618' OR sn7618 OR solprina OR solprine OR tresochin OR tresochine OR tresoquine OR trochin OR trochine OR troquine OR 'w 7618' OR w7618 OR 'win 244' OR win244 OR 'antimalarial agent'/exp OR 'antimalarial agent' OR 'anti malaria drug'/exp OR 'anti malaria drug' OR 'antimalaria agent'/exp OR 'antimalaria agent' OR 'antimalaria drug'/exp OR 'antimalaria drug' OR 'antimalaria drug, synthetic'/exp OR 'antimalaria drug, synthetic' OR 'antimalarial'/exp OR antimalarial OR 'antimalarial drug'/exp OR 'antimalarial drug' OR 'antimalarials'/exp OR antimalarials OR 'antipaludean agent'/exp OR 'antipaludean agent' OR 'antiplasmodic agent'/exp OR 'antiplasmodic agent' OR 'synthetic antimalaria agent'/exp OR 'synthetic antimalaria agent' #3 #1 AND #2 #4 #3 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	
LILACS	#1 MH:"Coronavirus" OR MH:B04.820.504.540.150$ OR (Coronavirus) OR "COVID-19" OR (COVID) OR (SARS-CoV-2) OR (Deltacoronavirus) OR (Coronaviruses)	0

Chart 1. Search strategies for electronic databases and other sources (conclusion)

	#2 MH:"Hydroxychloroquine" OR MH:"Hidroxicloroquina" OR MH:D03.633.100.810.050.180.350$ OR (Hydroxychloroquine) OR (Hidroxicloroquina) OR (Hydroxychlorochin) OR (Hydroxychloroquine Sulfate) OR "Hydroxychloroquine Sulfate (1:1) Salt" OR (Oxychlorochin) OR (Oxychloroquine) OR (Plaquenil) OR (Oxicloroquina) OR MH:"Cloroquina" OR MH:"Chloroquine" OR MH:D03.633.100.810.050.180$ OR (Cloroquina) OR (Chloroquine) OR (Aralen) OR (Arechine) OR (Arequin) OR (Chingamin) OR (Chlorochin) OR (Chloroquine Sulfate) OR (Chloroquine Sulphate) OR (Khingamin) OR (Nivaquine) OR (Sulfate, Chloroquine) OR (Sulphate, Chloroquine) OR MH:"Antimaláricos" OR MH:"Antimalarials" OR MH:D27.505.954.122.250.100.085$ OR (Antimaláricos) OR (Antimalarials) OR (Agents, Antimalarial) OR (Anti Malarials) OR (Anti-Malarials) OR (Antimalarial Agents) OR (Antimalarial Drugs) OR (Drugs, Antimalarial) #3 #1 AND #2	
MEDLINE	#1 "Coronavirus"[Mesh] OR "COVID-19" OR (COVID) OR (Coronavirus) OR (SARS-CoV-2) OR (Coronaviruses) OR (Deltacoronavirus) OR (Deltacoronaviruses) OR "Munia coronavirus HKU13" OR (Coronavirus HKU15) OR (Coronavirus, Rabbit) OR (Rabbit Coronavirus) OR (Coronaviruses, Rabbit) OR (Rabbit Coronaviruses) OR "Bulbul coronavirus HKU11" OR "Thrush coronavirus HKU12" #2 "Hydroxychloroquine"[Mesh] OR (Hydroxychloroquine) OR (Oxychlorochin) OR (Oxychloroquine) OR (Hydroxychlorochin) OR (Plaquenil) OR (Hydroxychloroquine Sulfate) OR "Hydroxychloroquine Sulfate (1:1) Salt" OR (Hidroxicloroquina) OR (Hydroxychloroquine) OR (Hydroxychloroquinum) OR (Oxichlorochine) OR (Oxichloroquine) OR "Chloroquine"[Mesh] OR Chlorochin OR Cloroquina OR Cloroquine OR Chloroquine OR "Antimalarials"[Mesh] OR (Antimalarials) OR (Antimalarial Agents) OR (Agents, Antimalarial) OR (Antimalarial Drugs) OR (Drugs, Antimalarial) OR (Anti-Malarials) OR (Anti Malarials) OR "(N4-(7-Chloro-4-quinolinyl)-N1,N1-diethyl-1,4-pentanediamine)" OR Hydroquin OR Axemal OR Dolquine OR Quensyl OR Quinoric #3 #1 AND #2	54
Opengrey	#1 "COVID-19" OR (COVID) OR (Coronavirus) OR (SARS-CoV-2) OR (Coronaviruses) OR (Deltacoronavirus) OR (Deltacoronaviruses)	76
ClinicalTrials.gov	#1 "COVID-19" OR (COVID) OR (Coronavirus) OR (SARS-CoV-2) OR (Coronaviruses) OR (Deltacoronavirus) OR (Deltacoronaviruses) #2 Hydroxychloroquine OR Oxychlorochin OR Oxychloroquine OR Hydroxychlorochin OR Plaquenil OR Chlorochin OR Cloroquina OR Cloroquine OR chloroquine OR Antimalarials OR Antimalarial #3 #1 AND #2	12
WHO-ICTRP	#1 "COVID-19" OR (COVID) OR (Coronavirus) OR (SARS-CoV-2) OR (Coronaviruses) OR (Deltacoronavirus) OR (Deltacoronaviruses) #2 Hydroxychloroquine OR Oxychlorochin OR Oxychloroquine OR Hydroxychlorochin OR Plaquenil OR Chlorochin OR Cloroquina OR Cloroquine OR chloroquine OR Antimalarials OR Antimalarial #3 #1 AND #2	33

LILACS: Literatura Latino-Americana e do Caribe em Ciências da Saúde; MEDLINE: Medical Literature Analysis and Retrieval System Online; WHO-ICTRP: World Health Organization - International Clinical Trials Register Platform.

Manual search

A manual search was performed on the reference lists of the relevant studies.

Study selection and data extraction

The process to select the studies was performed by two independent review authors and disagreements were solved by consensus. Study selection was conducted in two steps. The first step consisted in the screening of titles and abstracts of all retrieved references. The potentially eligible references were read in full (second stage), to confirm their eligibility. The entire process was performed using Rayyan platform (https://rayyan.qcri.org)[6]. The procedures for data extraction were conducted by two independent review authors as well.

Methodological quality/risk of bias assessment

The methodological quality/risk of bias assessment of the included studies was performed using appropriate tools for each study design, as following:

- Randomized controlled trial: Cochrane Risk of Bias Table[4].
- Non-randomized controlled trial or quasi-randomized: ROBINS-I[7].
- Longitudinal comparative observational studies (case-control and cohort): Newcastle-Ottawa[8].
- For phase 1/2 clinical trials without a direct comparator arm, it would be used an adapted version of the Cochrane Risk of Bias Table[4], as they are not validated tools for this study design.

Unity of analysis

The unit of analysis was the individual.

Measures of treatment effect and analysis procedures

According to data availability and homogeneity of studies, we would pool results by including studies through random-effects meta-analysis (quantitative synthesis). Risk ratios and mean differences would be calculated to assess dichotomous and continuous variables, respectively. A 95% confidence interval would be considered in the analysis. The software used to perform all analysis would be Review Manager 5.3 software. However, in this review, meta-analyses were not possible (data availability or heterogeneity of studies - reasons detailed under results section), then results were presented narratively (qualitative synthesis) considering the effect size estimates (relative risk, absolute risk difference, hazard ratio, odds ratio, number needed to treat and others) and their respective confidence or variance measures (dispersion measures, confidence intervals and p values).

Investigating heterogeneity

Methodological and clinical diversity of included studies were considered when deciding conduct or not quantitative synthesis. The statistical heterogeneity would be considered by means of a Chi^2 test ($p<0.1$ was used as a significance cut-off) and I^2 test ($I^2>50\%$ would be used as an indicative of high inconsistency among studies). Subgroup analyses were planned to explore reasons for heterogeneity and its impacts would be discussed.

Additional analyses

We planned to perform the following additional analyses, but it was not possible due to the scarcity of data for quantitative synthesis.

Sensitivity analyses

a) Fixed-effect versus random effects model meta-analysis. When the results of fixed effect meta-analysis led to a different result, both would be reported.
b) Excluding from analysis studies at high risk of bias
c) Excluding from analysis studies with industry sponsorship.

Subgroup analysis

a) Severity of COVID-19 infection
b) Age of participants
c) Co-morbidity of participants (diabetes, cardiac conditions, immunosuppression, HIV)

Publication bias assessment

Investigation of publication bias assessment was planned to be performed by visual inspection of funnel plots, if more than 10 studies were included in a single meta-analysis.

Missing data

Authors from primary study were not contacted for missing data, taking into account the context underpinning a rapid systematic review. When necessary, missing standard deviations would be calculated using reported confidence intervals and/ or standard mean errors.

Assessing the certainty of evidence

To assess the certainty of evidence, we used the GRADE approach[9] for the clinical relevant outcomes and a summary of findings table would be presented using the GRADEpro GDT platform.

Results

Search Results

The search strategies retrieved 223 references. After reading the title and abstract (first step), seven duplicate references (identical references) and 186 references in disagreement with PICOS were eliminated. Reading the full text of the 30 selected references confirmed the eligibility (second stage). The flowchart of the selection process is shown in Figure 1. After the selection process, 30 studies were included:

- a randomized clinical trial published in Chinese (the translation into English was used to carry out the analyzes of this review)[10].
- a non-randomized ongoing clinical trial, with partial results[11].
- 28 ongoing clinical studies (Chart 2).

Chart 2. Characteristics and methodological aspects of the ongoing studies (to be continued)

Study	Status	Estimate start/end date	Design	Participants (n)	Intervention	Comparators	Main interest outcomes	Funding
NCT04307693	Recruiting	11 March 2020/ May 2020	RCT	Participants with confirmed COVID-19 diagnosis (150)	Hydroxychloroquine	Lopinavir/ritonavir No intervention	Laboratory detection/viral load Time to clinical improvement Time to death Intensive unit care or mechanical ventilation Progression to oxygen supplementation	Asan Medical Center
NCT04318444	Not yet recruiting	March 2020/March 2020	RCT	Participants that had household or in-hospital contact with COVID-19 patients (1600)	Hydroxychloroquine	Placebo	Confirmed COVID-19 cases Cases with symptoms of COVID-19	Columbia University
NCT04303507	Not yet recruiting	April 2020/April 2021	RCT	Participants without previous cCOVID-19 diagnosis (40000)	Hydroxychloroquine /Chloroquine	Placebo	Duration of COVID-19 infection Number of asymptomatic cases Number of symptomatic cases Symptom severity	University of Oxford
NCT04315896	Not yet recruiting	23 March 2020/22 March 2021	RCT	Participants with confirmed COVID-19 diagnosis and serious respiratory impairment (500)	Hydroxychloroquine	Placebo	All-cause mortality Length of hospitalization Mechanical ventilation	Sanofi

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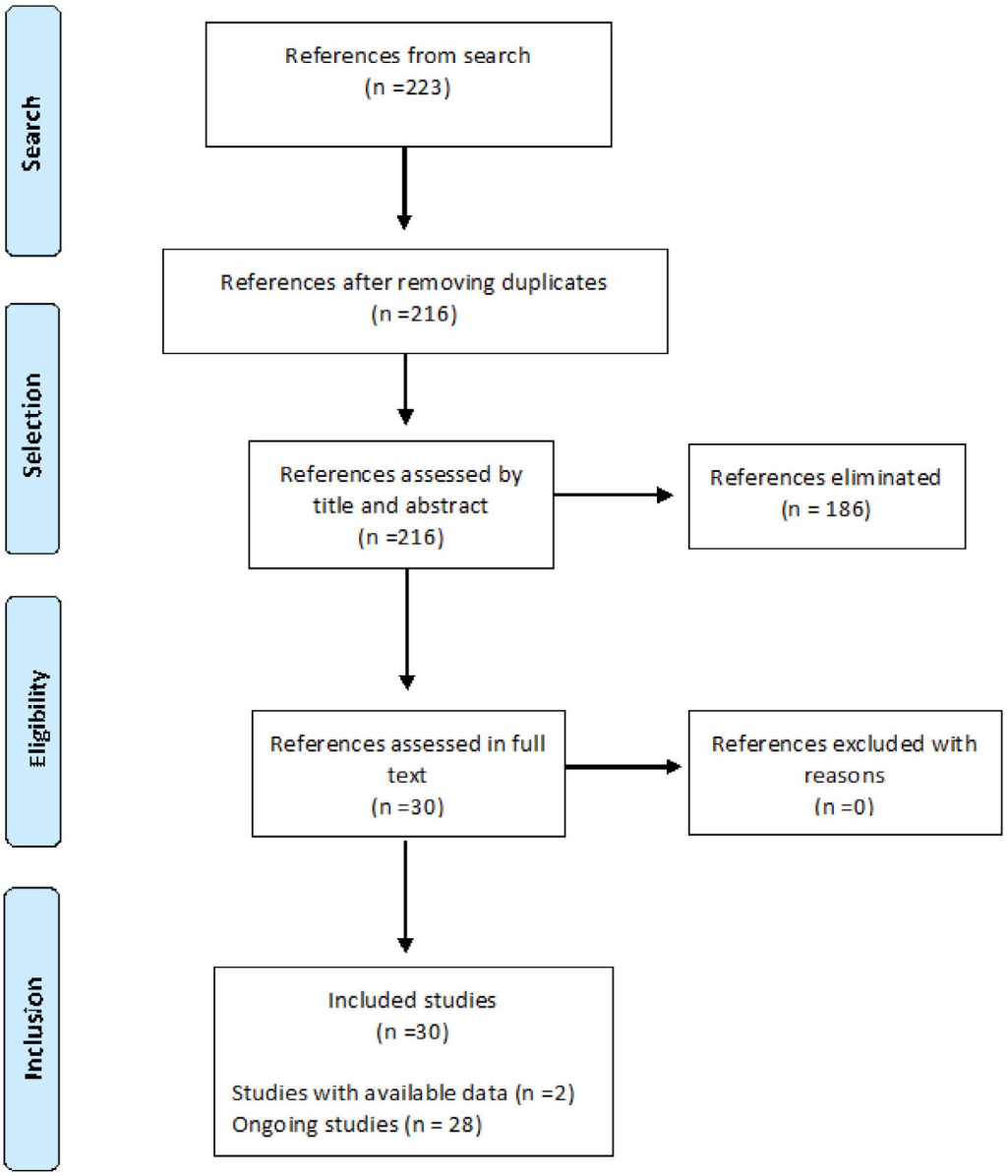
Chart 2. Characteristics and methodological aspects of the ongoing studies (continuation)

Study	Status	Estimate start/end date	Design	Participants (n)	Intervention	Comparators	Main interest outcomes	Funding
NCT04323631	Not yet recruiting	March 2020/December 2020	RCT	Participants with confirmed COVID-19 diagnosis (1116)	Hydroxychloroquine	No intervention	Number of participants with severe infection or death	Rambam Health Care Campus
NCT04318015	Not yet recruiting	01 April 2020/ 31 March 2021	RCT	Health professionals that had contact with COVID-19 patients (400)	Hydroxychloroquine	Placebo	Number of symptomatic cases Absenteeism Complications	National Institute of Respiratory Diseases, Mexico / Sanofi
NCT04316377	Not yet recruiting	23 March 2020/25 March 2023	RCT	Participants with confirmed COVID-19 diagnosis, hospitalized and with serious respiratory impairment (202)	Hydroxychloroquine	Usual treatment	Mortality Length of hospitalization Mechanical ventilation Length of ICU stay Laboratory detection/viral load	University Hospital, Akershus
NCT04319900	Recruiting	5 March 2020/ 25 June 2020	RCT	Participants with confirmed COVID-19 diagnosis (100)	Chloroquine + Favipiravir	Favipiravir	Time to symptom improvement	Beijing Chao Yang Hospital
NCT04321616	Not yet recruiting	26 March 2020/November 2020	RCT	Hospitalized participants with confirmed COVID-19 diagnosis (700)	Hydroxychloroquine	Remdesivir No intervention	All-cause mortality Intensive unit care Mechanical ventilation	Oslo University Hospital
NCT04308668	Recruiting	17 March/May 2020	RCT	Participants that were exposed to a COVID-19 patient (3000)	Hydroxychloroquine	Placebo	Confirmed COVID-19 cases Severity of COVID-19 infection Hospitalization Mortality	University of Minnesota
NCT04321993	Not yet recruiting	March 2020/ June 2021	nRCT	Hospitalized participants with confirmed COVID-19 diagnosis with moderate/severe diasease (1000)	Hydroxychloroquine	Lopinavir/ritonavir Baricitinib Sarilumab	Clinical status Mortality Length of disease	Nova Scotia Health Authority
ChiCTR2000030718	Recruiting	Not reported	RCT	Participants with confirmed COVID-19 diagnosis (80)	Hydroxychloroquine	No intervention	Mortality Severity of respiratory impairment Length of disease Laboratory detection/viral load Oxygen supplementation duration	Hubei Clinical Research Center for Emergency and Resuscitation
ChiCTR2000029988	Recruiting	Not reported	RCT	Participants with confirmed COVID-19 diagnosis and severe disease (80)	Chloroquine	No intervention	All-cause mortality Length of hospitalization Length of ICU stay Length of mechanical ventilation	Hubei Clinical Research Center for Emergency and Resuscitation
ChiCTR2000029939*	Recruiting	Not reported	RCT	Participants with confirmed COVID-19 diagnosis (100)	Chloroquine	No intervention	Specific mortality Length of hospitalization	HwaMei Key Research Fund (2020HMZD18)
ChiCTR2000029935*	Recruiting	Not reported	Single arm study	Participants with confirmed COVID-19 diagnosis (100)	Chloroquine	NA	Specific mortality específica	HwaMei Key Research Fund (2020HMZD18)

Chart 2. Characteristics and methodological aspects of the ongoing studies (conclusion)

Study	Status	Estimate start/end date	Design	Participants (n)	Intervention	Comparators	Main interest outcomes	Funding
ChiCTR2000029899/ ChiCTR2000029898	Recruiting	Not reported	RCT	Participants with confirmed COVID-19 diagnosis (100)	Hydroxychloroquine	Chloroquine	Length of disease All-cause mortality	Peking University Third Hospital
ChiCTR2000029868	Recruiting	Not reported	RCT	Participants with confirmed COVID-19 diagnosis (200)	Hydroxychloroquine	No intervention	Laboratory detection/viral load	SPH SHANGHAI ZHONGXI PHARMACEUTICAL CO., LTD
ChiCTR2000029741	Recruiting	Not reported	RCT	Participants with confirmed COVID-19 diagnosis (112)	Hydroxychloroquine	Lopinavir / Ritonavir	Length of hospitalization Proportion of critical cases All-cause mortality	Sun Yat-Sen University
ChiCTR2000029740	Recruiting	Not reported	RCT	Participants with confirmed COVID-19 diagnosis (78)	Hydroxychloroquine	No intervention	Laboratory detection/viral load	The First Hospital of Peking University
ChiCTR2000029559	Recruiting	Not reported	RCT	Participants with confirmed COVID-19 diagnosis (200)	Hydroxychloroquine	Placebo	Laboratory detection/viral load	Renmin Hospital of Wuhan University
ChiCTR2000029542	Recruiting	Not reported	RCT	Participants with confirmed COVID-19 diagnosis (20)	Chloroquine	No intervention	All-cause mortality Length of ICU stay Length of hospitalization	Sun Yat sen Memorial Hospital of Sun Yat sen University
NCT04321278	Not yet recruiting	23 March 2020/30 August 2020	RCT	Participants with likely or confirmed COVID-19 diagnosis (440)	Hydroxychloroquine	Hydroxychloroquine + Azithromycin	Clinical status All-cause mortality Length of hospitalization Number of days without mechanical ventilation	Hospital Israelita Albert Einstein
NCT04303299	Not yet recruiting	15 March 2020/30 November 2020	RCT	Participants with confirmed COVID-19 diagnosis (80)	Oseltamivir + Chloroquine	Different schemes of Oseltamivir, Darunavir, Lopinavir and Faviparivir	Laboratory detection/viral load Mortality Length of mechanical ventilation	Rajavithi Hospital
NCT04322123	Not yet recruiting	6 April 2020/30 August 2020	RCT	Participants with likely or confirmed COVID-19 diagnosis (630)	Hydroxychloroquine	Hydroxychloroquine + Azithromycin	Clinical status All-cause mortality Length of hospitalization Proportion of patients with orotracheal intubation	Hospital do Coração
NCT04324463	Not yet recruiting	1 April 2020/30 September 2020	RCT	Participants with confirmed COVID-19 diagnosis (1500)	Chloroquine + Azithromycin	No intervention	Hospitalization or death Mechanical ventilation or death	Population Health Research Institute
NCT04304053	Recruiting	18 March 2020/15 June 2020	RCT	Participants with confirmed COVID-19 diagnosis (3040)	Hydroxychloroquine + Darunavir	No intervention	Incidence of COVID-19 in close contacts	Fundacio Lluita Contra la SIDA
NCT04322396	Not yet recruiting	1 April 2020/31 October 2020	RCT	Participants with confirmed COVID-19 diagnosis (226)	Hydroxychloroquine + Azithromycin	Placebo	Clinical status Mortality Length of hospitalization	Chronic Obstructive Pulmonary Disease Trial Network, Denmark
NCT04323527	Recruiting	23 March 2020/31 August 2020	RCT	Participants with likely or confirmed COVID-19 diagnosis (440)	Chloroquine (high dosage)	Chloroquine (low dosage)	Mortality Length of hospitalization Length of mechanical ventilation	Fundação de Medicina Tropical Dr. Heitor Vieira Dourado

Figure 1. Flowchart of the study selection



Main findings and methodological characteristics of the two clinical studies with available results are depicted in Chart 3. Details of the 28 ongoing studies are presented in the Chart 2.

The two included studies evaluated the same primary outcome (viral detection), in a similar follow-up (6 and 7 days)[10,11]. However, we did not consider appropriate to perform a quantitative synthesis of its results (meta-analysis) due to the following aspects related to the clinical and methodological heterogeneity between the studies:

- Different study design: randomized clinical trial[10] and non-randomized clinical trial[11].
- Different methods of data analysis: intention-to-treat[10] and per protocol[11].
- Different hydroxychloroquine dosage and treatment duration: 400mg/day for five days[10] and 600mg/day for 10 days[11].
- Difference in the mean age of participants in the control group: 50.5±3.8[10] and 37.3 ± 24.0[11]. The difference in the standard deviation between the groups also shows that the age dispersion was lower in Chen 2020, increasing heterogeneity between the samples from the two studies.
- Differences in the frequency of the primary outcome in the control groups: 93.3%[10] and 12.5%[11]. This difference may indicate that the population from both studies were not similar and/or the co-interventions used were different, impacting on the effects observed from the intervention.
- Differences in co-interventions allowed during the study conduction.

Chart 3. Main findings and methodological characteristics of the included studies (to be continued)

Study	Chen 2020[10]	Gautret 2020[11]
Design	Open-label randomized clinical trial (NCT04261517)	Open label non- randomized clinical trial (EU Clinical Trials Register 2020-000890-25)
Population /condition of interest	• Hospitalized patients with documented diagnosis of COVID-19 infection • > 18 years old	• Hospitalized patients with documented diagnosis of COVID-19 infection • > 12 years old
Interventions	• Hydroxychloroquine 400mg / 1x day for 5 days (n = 15) • Standard treatment (n = 15)	• Hydroxychloroquine 200mg - 3 times / day for 10 days (n = 20) • Hydroxychloroquine 200mg - 3 times / day for 10 days associated with azithromycin (500mg 1x / day + 250mg / day for 4 days) (n = 6) Standard treatment (n = 16)
Funding	Shanghai Public Health Clinical Center	French Government
Negative viral load in oropharyngeal swab by PCR	• After 7 days of treatment: 86.7% (13/15) in the hydroxychloroquine group had negative viral detection *versus* 93.3% (14/15) in the control group (p> 0.05) • After 14 days, all 30 patients had a negative test.	• After 6 days of treatment: 70% of the hydroxychloroquine group had no viral detection versus 12.5% in the control group (p = 0.001) • Post-hoc analysis: 100% of the hydroxychloroquine + azithromycin group (n = 6) had no viral detection *versus* 57.1% in the hydroxychloroquine group *versus* 12.5% in the standard treatment group.
Adverse events	• Hydroxychloroquine group: four events: ○ Diarrhea (n = 2) ○ Worsening of the clinical condition with discontinuation of treatment (n = 1) ○ Transient increase in aspartate aminotransferase (n = 1) • Standard treatment group: 3 events ○ Increase in serum creatinine (n = 1) ○ Anemia (n = 1) ○ Transient increase in aspartate aminotransferase (n = 1).	Not assessed
Time to negative viral load (PCR)	• Hydroxychloroquine group: median 4 days (1st quartile = 1; 3rd quartile = 9) • Standard treatment group: Median 2 days (1st quartile = 1; 3rd quartile = 4).	Not assessed

Chart 3. Main findings and methodological characteristics of the included studies (conclusion)

Study	Chen 2020[10]	Gautret 2020[11]
Radiological progression	• Hydroxychloroquine group: 33% (5/15) presented radiological improvement after 3 days of follow-up and 100% after 14 days. • Standard treatment: 46.7% presented radiological improvement (7/15) after 3 days of follow-up and 100% after 14 days.	Not assessed
Mortality	There were no deaths in either intervention groups at 14 days of follow-up	Not reported
Risk of bias	High risk of performance bias and unclear risk of selection and detection bias	Overall risk of bias: serious

PCR: polymerase chain reaction

Risk of bias assessment of the included studies

The risk of bias assessment of the included studies and all justifications for each judgment is presented in Charts 4 and 5.

Chart 4. Risk of bias of the included randomized clinical trial[10], using the Cochrane Risk of Bias Table[4]

Domain	Judgment	Commentaries and justifications
Random sequence generation	Unclear	Not reported
Allocation concealment	Unclear	Not reported
Blinding of participants and personnel	High risk	Open label study
Blinding of outcome assessors	Unclear	It is not clear if the outcome assessor was blinded.
Incomplete outcome data	Low	Only one participant in the intervention arm had to stop taking hydroxychloroquine due to adverse events. The authors performed an intention- to-treat analysis.
Selective outcome reporting	Low	The clinicaltrials.gov registry (NCT04261517) was published on 7th February, 2020 and the enrollment period was from 6th February 2020 to 25th February 2020. Despite this delay in one day in the registry, considering the number of participants and the extension of the enrollment period it was considered that this registry was prospective. The primary outcomes were pre-planned and reported in the manuscript.
Other bias	Low	We did not identify any other apparent source of bias.

Chart 5. Risk of bias of the non-randomized clinical trial[11], using the ROBINS-II[2]

Domain	Judgment	Commentaries and justifications
Bias due to confounding	Serious	The baseline mean age of the participants in the hydroxychloroquine group was 51.2 years (standard deviation 18.7) and 37.3 (standard deviation 24.0) in the control group. The authors reported a p value = 0.06. However, this is an important imbalance in this prognosis factor. The fact that the mean age was higher in the intervention group may indicate that it was preferred to include patients with higher risk factors in the intervention group.
Bias in selection of participants into the study	Serious	The intervention group was recruited in a single centre (*"The Méditerranée Infection University Hospital Institute in Marseille")* and the control group was recruited in other centres ("*Controls without hydroxychloroquine treatment were recruited in Marseille, Nice, Avignon and Briançon centers, all located in South France*"). It is also stated that patients in the Marseille group that refused consent or were not eligible to receive hydroxychloroquine were used as controls. This characteristic increases the risk of bias expressively, because co-interventions and the conditions of each centre can be very distincts, generating an imbalance in the baseline and during the evolution of the study.
Bias in classification of interventions	Low	This was a prospective study. The risk of bias related to classification of interventions is low.
Bias due to deviations from intended interventions	Serious	This was an open-label study. Six patients in the hydroxychloroquine (23%) also received azithromycin. Besides that, co-interventions were not controlled and probably not homogenous between the arms of the trial.
Bias due to missing data	Serious	Six patients in the hydroxychloroquine (23%) group were not analyzed for the reported outcome. Despite being reported as "losses to follow-up", the authors performed a *per protocol* analysis.
Bias in measurement of outcomes	Moderate	It was not clear if the outcome assessor was blinded. Despite the outcome is laboratorial, the procedures to collect the samples may be different and influenced by the enrolment awareness.
Bias in selection of the reported result	Serious	Planned outcomes were not reported and the time point reported in the study (6 days) was not planned in the protocol [EU Clinical Trials Register 2020-000890-25].
Overall bias	Serious	The study was considered to be at serious risk of bias in five domains.

Assessment of the evidence certainty

We used the GRADE approach to assess the evidence provided by the randomized clinical trial included in this review (Table 1). For all considered outcomes, the evidence was graded as very low certainty (downgraded two levels due to imprecision and two levels due to risk of bias). This means that we are uncertain regarding any effect that hydroxychloroquine may have in COVID-19 patients, and future studies are likely to change any efficacy and safety estimates reported by the study.

Table 1. Summary of findings table (Hydroxychloroquine versus no treatment) (to be continued)

Summary of findings:

Hydroxychloroquine compared to no treatment for COVID-19

Patient or population: COVID-19

Setting: Hospitalized patients

Intervention: Hydroxychloroquine

Comparison: No treatment (standard care)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with No treatment	Risk with Hydroxychloroquine				
Mortality related to COVID-19 follow up: 14 days	-	-	-	30 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	The authors reported no deaths in both groups at 14 days of follow-up.
Severe adverse events - not reported	-	-	-	-	-	
Progression to COVID-19 acute respiratory syndrome (SARS-Cov-2) - not reported	-	-	-	-	-	
All-cause mortality	-	-	-	30 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	The authors reported no deaths in both groups at 14 days of follow-up.
Admission to an intensive care unit - not reported	-	-	-	-	-	
Any adverse event	-	-	-	30 (1 RCT)	⨁◯◯◯ VERY LOW [a,c]	There were three minor adverse events on control group (creatinine increase, anemia, aspartate aminotransferase elevation) and four minor adverse events on intervention group (two diarrhea, one treatment discontinuation due to deterioration in clinical status and one aspartate aminotransferase elevation)
Health-related quality of life - not reported	-	-	-	-	-	

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Table 1. Summary of findings table (Hydroxychloroquine versus no treatment) (continuation)

Summary of findings:

Hydroxychloroquine compared to no treatment for COVID-19

Patient or population: COVID-19

Setting: Hospitalized patients

Intervention: Hydroxychloroquine

Comparison: No treatment (standard care)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with No treatment	Risk with Hydroxychloroquine				
Laboratory outcomes - Viral detection assessed with: Polymerase chain reaction follow up: 7 days	-	-	-	30 (1 RCT)	⨁◯◯◯ VERY LOW [a,c]	86.7% (13/15) in the hydroxychloroquine group had negative viral detection versus 93.3% (14/15) in the control group (p> 0.05). The non-randomized controlled trial included in this review reported that, at 6 days, 70% of the hydroxychloroquine group had no viral detection versus 12.5% in the control group (p = 0.001).
Laboratory - Infection duration assessed with: Days until negative PCR follow up: 7 days	-	-	-	30 (1 RCT)	⨁◯◯◯ VERY LOW [a,c]	Hydroxychloroquine group had a median infection duration of 4 days (1st quartile = 1; 3rd quartile = 9) compared to 2 days (1st quartile = 1; 3rd quartile = 4) in the control group.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

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Table 1. Summary of findings table (Hydroxychloroquine versus no treatment) (conclusion)

Summary of findings:

Hydroxychloroquine compared to no treatment for COVID-19

Patient or population: COVID-19

Setting: Hospitalized patients

Intervention: Hydroxychloroquine

Comparison: No treatment (standard care)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with No treatment	Risk with Hydroxychloroquine				

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded two levels because of high risk of performance bias and unclear risk of detection and selection bias

b. Downgraded two levels because of imprecision (Small study, with no events on both arms)

c. Downgraded two levels because of imprecision (Small study with 30 patients)

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Discussion

Although experimental *in vitro* studies suggest potential antiviral action of hydroxychloroquine against COVID-19[12,13], and health authorities are recommending this drug for patients with COVID-19 infection, this rapid systematic review identified mere two studies with available data addressing this question: one open-label non-randomized trial with 42 participants[11] and one open-label randomized trial with 30 participants[10]. These studies present high risk of bias and their results were inconsistent about the only common outcome between them (viral load detection).

There are currently 58 cataloged biases that can contribute to the results of clinical studies to distance themselves from the truth[14,15]. In order to have reliable and applicable results, it is expected that rigorous methods will be adopted by studies to prevent the occurrence of these biases during the planning, conducting and reporting phases. However, this methodological rigor, already known since the conduct of the first clinical trial, was not adopted by the two studies presented.

The presence of a similar comparator group (which probably did not occur in the studies) is essential to estimate the real effects of hydroxychloroquine and to assess whether these effects are different from those observed using the best available option, placebo or natural course of the disease. This similarity also contributes to assure that the estimated effect may be due exclusively to the intervention, eliminating the effect of confounding factors present at different levels in the compared groups, such as disease severity, age or comorbidities. An appropriate randomization method would avoid this confusion. Although the Chen 2020 study is described as randomized, details of randomization and methods to maintain allocation concealment were not presented by the authors.

The absence of adequate methods for allocation concealment could overestimate the effect of the intervention by 37% to 41%[16]. That is, depending on the size of the effect, an estimate that means a benefit may actually be wrong.

The lack of masking of participants, personnel and outcomes assessors can lead to deviations in the process of conducting the study (such as impacting on the adherence to treatment and notification of adverse events) and in the process of evaluating the outcomes.

The existence of favorable recommendations from some parties involved in the decision-making process regarding the use of hydroxychloroquine underscores the importance of the results of ongoing trials so that the effects of hydroxychloroquine for patients with COVID-19 are known. This is a point that needs to be addressed in a context where there is an urgent need for answers. As this review identified 28 approved clinical trial records in progress on the two largest clinical trial platforms (Clinicaltrials.gov and ICTRP-WHO), more data will be available soon.

Finally, the justification for the use of drugs for cases of COVID-19, as well as for any other disease, must be based on the existence of clinical benefits (reduced mortality, and respiratory complications for example) observed through reliable clinical studies, preferably randomized, double-blind clinical trials.

The use of a drug should not be justified solely by its potential mechanisms of action observed in experimental / preclinical studies. Recent examples, such as the use of albumin in large burns, have already shown that this is not an acceptable strategy when the objective is to offer a treatment with a better probability of benefits than harms.

Ignoring these precepts certainly increases uncertainty in decision-making - which means the exact opposite of what clinical research has sought to follow, more rigorously, over the past 25 years. Thus, in view of the alarming current scenario, it is essential that decisions are informed by the best available evidence, so that today's actions are more likely to bring benefits than harms to the population.

As implication for practice, this review did not find sufficient evidence to support the use of hydroxychloroquine or chloroquine as a routine for treating all patients with COVID-19, neither for preventive purposes. The exceptional prescription should be restricted for those patients with severe cases of COVID-19 infection, who are not at increased risk of adverse events associated with the use of hydroxychloroquine, and within a context of scientific investigation.

Conclusion

This rapid systematic review identified two clinical studies (with available data), with limited methodological quality, that evaluated the effects of hydroxychloroquine for COVID-19. Based on the findings of these studies, the efficacy and safety of hydroxychloroquine and chloroquine in patients with COVID-19 is still uncertain and its routine use for this situation should not be recommended until the results of ongoing studies could provide a proper assessment of their effects.

Author contributions

Both authors designed and performed the review, wrote the report and approved the final version.

Competing interests

No financial, legal or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).

References

1. China law translate. Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (Provisional 7th Edition). [Internet]. 2020. [acesso em 2020 mar. 26]. Disponível em: https://www.chinalawtranslate.com/coronavirus-treatment-plan-7/

2. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America. 2020. doi: 10.1093/cid/ciaa237

3. Sung-sun K. Physicians work out treatment guidelines for coronavirus". m.koreabiomed.com (in Korean). [Internet]. 2020. [acesso em 2020 mar. 26]. Disponível em: http://m.koreabiomed.com/news/articleView.html?idxno=7428.

4. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ et al (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). [Internet]. 2019. [acesso em 2020 mar. 26]. Disponível em: www.training.cochrane.org/handbook

5. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;21;6(7):e1000097. doi: 10.1371/journal.pmed.1000097

6. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan — a web and mobile app for systematic reviews. Syst. Rev. 2016;5(1):210. doi: 10.1186/s13643-016-0384-4

7. Stern JAC, Herńan MA, Reeves BC, Savoić J, Berkman ND, Viswanathan M et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of intervention. BMJ. 2016;355:i4919. doi: 10.1136/bmj.i4919

8. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. [Internet]. 2012. [acesso em 2020 mar. 26]. Disponível em: http://ohri.ca/programs/clinical_epidemiology/oxford.htm

9. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6. doi: 10.1136/bmj.39489.470347

10. Chen J, Liu D, Li Liu, LIU Ping,XU Qingnian,XIA Lu et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ (Med Sci). 2020;49(1). doi: 10.3785/j.issn.1008-9292.2020.03.03

11. Gautret P, Lagiera JC, Parola P, Hoang VT, Meddeba L, Mailhea M et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents. 2020. doi: 10.1016/j.ijantimicag.2020.105949

12. Gao J, Zhenxue T, Xu Y. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. BioScience Trends. 2020;14(1):72-73. doi: 10.5582/bst.2020.01047

13. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu Het al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;(6):16. doi: 10.1038/s41421-020-0156-0

14. Catalogue of Bias Collaboration. Catalogue Of Bias. [Internet]. 2020. [acesso em 2020 mar. 26]. Disponível em: https://catalogofbias.org/biases/attrition-bias/

15. Pacheco RL, Latorraca COC, Martimbianco ALC, Fontes LES, Vieira R, Miranda E et al. Translation of Oxford's CEBM catalogue of bias into Portuguese: contributing to the dissemination of conscientious thinking on health research. BMJ. 2020. doi: 10.1136/bmjebm-2019-111329

16. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA. 1995;273(5):408-12. doi: 10.1001/jama.273.5.408