AN UMBRELLA REVIEW OF SYSTEMATIC REVIEWS WITH META-ANALYSES EVALUATING POSITIVE AND NEGATIVE OUTCOMES OF HYDROXYCHLOROQUINE AND CHLOROQUINE THERAPY

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# ABSTRACT

**BACKGROUND & AIMS**: Hydroxychloroquine (HCQ) and chloroquine (CQ) are anti-malarial drugs frequently used in the rheumatologic field. Recently they were identified as possible therapeutic options against Coronavirus Disease (COVID-19). Therefore, the present study aimed to map and grade the diverse health outcomes associated with HCQ/CQ using an umbrella review approach.

**METHODS**: Umbrella review of systematic reviews of observational and intervention studies. For observational studies, random-effects summary effect size, 95% confidence interval, and 95% prediction interval were estimated. We also assessed heterogeneity, evidence for small-study effect and evidence for excess significance bias. The quality of evidence was then graded using validated criteria from highly convincing to weak. The evidence from randomized-controlled trials (RCTs) was graded using the GRADE tool.

**RESULTS**: From 313 articles returned, 6 meta-analyses were included (n=25 outcomes). Among meta-analyses of observational studies, HCQ/CQ is weakly associated with a reduced risk for cardiovascular events and diabetes when used for autoimmune diseases; it is also associated with higher risk of death when used for COVID-19 and with spontaneous abortion. Among meta-analyses of RCTs, HCQ/CQ is associated with an improvement of articular manifestations of the rheumatic diseases

**CONCLUSIONS**: There is high evidence of the efficacy of HCQ/CQ in the rheumatologic field. The lack of evidence for efficacy and risk of death associated with the use of HCQ/CQ for COVID-19, indicate the inappropriateness of its inclusion in recent COVID-19 therapy guidelines and urgent need for Randomised Controlled Trials to determine their eventual appropriateness as a therapy in that circumstance.

**Key words**: hydroxychloroquine; chloroquine; COVID-19; umbrella review.

# INTRODUCTION

Hydroxychloroquine/chloroquine (HCQ/CQ), a broadly used antimalarial medication, represents one of the most widely used immunosuppressor drugs in rheumatology ([Schrezenmeier and Dorner, 2020](#_ENREF_46)), being included in the therapeutic guidelines of systemic lupus erythematosus. ([Fanouriakis et al., 2019](#_ENREF_16)) and also considered for the treatment of other autoimmune diseases, such as antiphospholipid syndrome ([Tektonidou et al., 2019](#_ENREF_55)), Sjogren syndrome ([Ramos-Casals et al., 2020](#_ENREF_43)) and rheumatoid arthritis ([Smolen et al., 2020](#_ENREF_51)).

Recently, promising results from 15 trials reported by Chinese researchers indicate a possible role for HCQ/CQ with the new coronavirus disease (COVID-19). ([Yao et al., 2020](#_ENREF_63)) Despite the limited clinical data on the use of HCQ/CQ in COVID-19, the use of this drug is attracting considerable attention from the media. Individuals and lobby groups have called for widespread prescription of these drugs. ([Javelot et al., 2020](#_ENREF_31)) Moreover, advocacy actions that publicly endorsed the use of hydroxychloroquine and other medications (i.e. azithromycin) to treat COVID-19, made it become one of the most used treatments in this unprecedented pandemic. ([Ferner and Aronson, 2020](#_ENREF_17);[Jaffe, 2020](#_ENREF_30))

Currently, more than 200 trials of chloroquine, hydroxychloroquine, or both, sometimes in combination with other drugs, are registered worldwide. The translation from laboratory to clinic has also led to disappointments, probably due to the complex pharmacokinetics of 4 aminoquinolones, with scarce effects obtained so far. ([Ferner and Aronson, 2020](#_ENREF_17)) In some cell cultures chloroquine inhibits dengue, shows promising effects on ebola and influenza virus, has some effects on SARS-CoV2. ([Ferner and Aronson, 2020](#_ENREF_17);[Yao et al., 2020](#_ENREF_63))

From a public health perspective, the potential benefits as well as the uncontrolled and important side effects need to be considered before clinicians start exposing their patients to these drugs. A wide use of HCQ/CQ may expose some patients to harm, ranging from cutaneous adverse reactions to hepatic failure and ventricular arrhythmias, which occur especially when HCQ/CQ is associated with other medications, such as azithromycin. ([Ferner and Aronson, 2020](#_ENREF_17);[Mercuro et al., 2020](#_ENREF_38))

The aim of the present work is to evaluate - through an umbrella review- the strength and credibility of the evidence derived from systematic reviews with meta-analyses of observational and intervention studies regarding HCQ/CQ and obtain a general summary of their importance relative to health outcomes and side effects in previous research, in order to inform policies on its use in COVID-19.

# METHODS

The protocol for this review was registered in PROSPERO on 01st April 2020 in the context of the COVID-19 research and still waiting the formal approval. The submitted protocol is attached in the **Supplementary Material**.

## Data sources and searches

We conducted an umbrella review ([Ioannidis, 2009](#_ENREF_26)), searching the MEDLINE, Scopus, Embase databases from inception until 27th June 2020 with: “(Meta-Analysis [ptyp] OR metaanaly\*[tiab] OR meta-analy\*[tiab] OR Systematic review [ptyp] OR “systematic review” [tiab]) AND (Hydroxychloroquine [tiab] OR Hydroxychlorochin [tiab] OR “chloroquine” [tiab] OR Plaquenil [tiab] OR “Hydroxychloroquine Sulfate” [tiab] OR “Hydroxychloroquine Sulfate (1:1) Salt” [tiab]). We consequently hand-searched the reference lists of eligible articles and reviews in this field.

## Study selection

We considered eligible: 1. any meta-analysis (MA) that included people of any age, any risk category, any population, taking any HCQ/CQ medication; 2. meta-analyses of longitudinal design studies (i.e. prospective/ cohort or retrospective/ case-control) that investigated the association of HCQ/CQ administration with any outcome or meta-analyses of randomized controlled trials (RCTs) that investigated the effects of HCQ/CQ. The study selection was made by two authors independently (JD, SC). Disagreements were resolved through consensus with another independent author (NV). Full-texts of all potentially eligible articles were consequently evaluated by the same two authors (JD, SC) and any disagreement was resolved with another independent author (LS).

Meta-analyses were included only if they reported study-specific information (i.e. effect size, 95% confidence intervals [CIs], sample size) or if those metrics could be inferred from the data presented.

## Data extraction

For each eligible MA, two independent investigators (JD, SC) firstly extracted data from each eligible meta-analysis including the name of the first author, year of publication, study population, study design, outcome, number of studies, intervention, comparison, effect size reported with its 95% CI.

On a second phase the same two authors (JD, SC) extracted the following information for each original article: (I) PMID/doi; (II) meta-analysis author; (III) year of meta-analysis; (IV) first author name of single studies included in meta-analysis; (V) year of publication; (VI) population/main condition of patients exposed to HCQ/CQ; (VII) effect size metrics used in the meta-analysis; (VIII) study design of included primary studies (e.g. case-control, prospective, RCT); (IX) number of cases and controls for each study; (X) number of people treated with HCQ/CQ with the correspondent number of events and number of people in placebo/control and correspondent number of events in intervention meta-analyses; (XI) follow-up; (XII) mean age of participant population, (XIII) medication type (HCQ, CQ); (XIV) outcome.

Next, the study-specific estimated relative risk for any side effects or negative outcome (risk ratio [RR], odds ratio [OR], hazard ratio [HR], incident risk ratio, standardized mean differences [SMDs], mean differences [MD]), along with their 95% CIs, were extracted.

If two meta-analyses were available for the same outcome, the one included the largest in terms of studies considered and, if equal in terms of numerosity of studies, the most recent one was used. If there were observational and RCT meta-analyses investigating the same outcome, both were included.

## Outcomes

Any health outcome, adverse events and side effect potentially associated to HCQ/CQ therapy.

## Risk of bias assessment

The methodological quality of each included meta-analysis was assessed with the Assessment of multiple systematic reviews (AMSTAR) 2 tool (available at https://amstar.ca/Amstar-2.php), which is a recent update of AMSTAR, ([Shea et al., 2017](#_ENREF_49)) by two independent investigators (LS, SC). The AMSTAR2 ranks the quality of a meta-analysis from critically low to high according to 16 predefined items.

## Data synthesis and analysis

For each meta-analysis, we estimated the summary effect size and its 95% CIs through a random-effects model. We also estimated the prediction interval (PIs) and its 95% CI, which further accounts for between-study effects and estimates the certainty of the association if a new study addresses that same association. ([Higgins et al., 2009](#_ENREF_24);[IntHout et al., 2016](#_ENREF_25);[Serghiou and Goodman, 2018](#_ENREF_47)) Between-study inconsistency was estimated with the *I2* metric, with values > 50% indicative of high heterogeneity and > 75% very large heterogeneity. ([Higgins and Thompson, 2002](#_ENREF_23)) We calculated the evidence of small-study effects (i.e. whether small studies inflated effect sizes) using the regression asymmetry test ([Egger et al., 1997](#_ENREF_12)) with a p-value < 0**.**10. ([Carvalho et al., 2016](#_ENREF_8)) Finally, we applied the excess of significance test. ([Ioannidis and Trikalinos, 2007](#_ENREF_29)) Because of the limited statistical power of this test, a lenient significance threshold (p < 0.10) was adopted. ([Ioannidis, 2013](#_ENREF_27)) We considered the effect size of the largest dataset and based on this we estimated the power of each constituent study with an algorithm using a non-central *t* distribution. Excess significance for each meta-analysis was considered whenever p < 0**.**10.

We planned to run several sensitivity analyses (age, duration of therapy/exposure), but no sufficient data were available since these data were not sufficiently reported in the meta-analyses included, therefore hindering reliable analyses.

All statistical analyses were conducted in Stata, version 14.0 (StataCorp), and R, version 3.3.0 (R Foundation for Statistical Computing).

## Grading the evidence

For observational studies, using the criteria mentioned above, significant associations (i.e. p<0**.**05) were categorized into strong, highly suggestive, suggestive, or weak evidence, following a grading scheme that has already been applied in various fields. ([Theodoratou et al., 2014](#_ENREF_56);[Aromataris et al., 2015](#_ENREF_2);[Belbasis et al., 2016](#_ENREF_3);[Bellou et al., 2016](#_ENREF_4);[Dinu et al., 2017](#_ENREF_11);[Kyrgiou et al., 2017](#_ENREF_35);[Li et al., 2017](#_ENREF_36);[Veronese et al., 2018](#_ENREF_57);[Solmi et al., 2020](#_ENREF_52))

Moreover, GRADE assessment of observational studies was performed (supplementary table x GRADE of observational studies).

Based on GRADE assessment of observational studies (mostly case control), independently from significance of association, 1 was rated as moderate (Singh et al), nine were rates as low and all the remaining as very low quality. The rating was impaired mostly due to heterogeneity, unavailable data and quality assessment of original studies.

Evidence from meta-analyses of RCTs was assessed in terms of the significance of the summary effect, using a p-value <0**.**05 as the threshold for statistical significance. When the p-value for the random effect was <0**.**05, we evaluated the evidence using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) assessment. ([Guyatt et al., 2008](#_ENREF_20)) We also reported 95% PIs (excluding the null or not), the presence of large heterogeneity (I2 >50%), small study effects (P>0**.**10), and excess significance (P>0**.**10) as possible indicators of quality of the available evidence.

# RESULTS

## Literature review

The initial search yielded 313 articles. After duplicates (61) were removed, we started our selection and evaluated 252 papers. Only 62 papers were eligible for full text screening. As reported in the PRISMA flow-chart (**Figure 1**), we identified 6 meta-analyses as eligible ([Suarez-Almazor et al., 2000](#_ENREF_54);[Kaplan et al., 2016](#_ENREF_32);[Guillotin et al., 2018](#_ENREF_19);[Liu et al., 2018](#_ENREF_37);[Rempenault et al., 2018](#_ENREF_44);[Singh](#_ENREF_59) et al, 2020).

## Meta-analyses of observational studies

As shown in **Table 1**, the meta-analyses of the observational studies included 17 outcomes. Two outcomes included HCQ/CQ, whilst the other 15 included only HCQ. Most (16/17) of the outcomes included people with different autoimmune diseases, including those in pregnancy (n=10 outcomes). As a consequence, the obstetrical outcomes were the most frequently included. One last outcome was mortality in people with COVID-19. The median number of studies included was 5 (range: 2-10), the median number of events was 93 (range: 4-273) and the median sample size was 2,311 (range: 252-16,885).

Only four outcomes reported a high heterogeneity, with an *I2* between 50 and 75%. The small-study effect was present in 2/17 of the outcomes included, whilst no outcome presented excess significance bias. Four outcomes out of 17 presented the largest study in terms of participants statistically significant (p<0.05). No one of the outcomes included had the 95% PIs excluding the null.

Using the criteria mentioned before, 7/17 outcomes reported a statistically significant effect size (p<0.05) and were all rated as weak. One outcome reported a higher risk of death in people with COVID-19. Three outcomes reported a lower incidence of CVD in autoimmune diseases, one outcome showed a lower incidence of type 2 diabetes in rheumatoid arthritis and two outcomes revealed a higher rate of spontaneous abortion in women with autoimmune rheumatologic conditions.

## Meta-analyses of RCTs (vs. placebo)

Eight outcomes were explored by the RCTs taking placebo as control group. No outcome presented active medications as control group.

**Table 2** reports some descriptive findings regarding the meta-analyses of the RCTs. Only one condition was included, i.e. rheumatoid arthritis (n=8).

Four RCTs were included with a median number of participants of 528 (in median, 269 randomized to HCQ/CQ and 259 to placebo). The largest study was statistically significant in 4/8 outcomes and one outcome included a 95% PI statistically significant (i.e. lower number of swollen joints). Overall, 6/8 outcomes were statistically significant and, consequently, rated using the GRADE.

As shown in **Table 3**, we found that the use of HCQ/CQ compared to placebo was associated with an improvement of the measure of articular inflammation, i.e. a lower number of swollen joints (n=4 RCTs, MD= -3.71; 95%CI: -4.86 to -2.57) with a high certainty of evidence. Moreover, HCQ/CQ was associated, when compared to placebo, to a lower incidence of withdrawals and dropouts (OR=0.58; 95%CI: 0.40-0.86), and also to lower withdrawals and dropouts due to lack of efficacy (OR=0.54; 95%CI: 0.32-0.92). A moderate certainty of evidence was present for the improvement of the physician’s global assessment of the disease and of subjective measures of inflammation, the number of painful joints (namely, tender joints). A low grade of evidence was found for the patient’s global assessment of the disease.

## Risk of bias

The assessment of the risk of bias in the meta-analyses included is reported in **Supplementary Table 1**. Four meta-analyses were rated as critically low, whilst two low. The main reasons of this downgrading were the absence of a list of excluded studies (item 7), poor information regarding the source of funding in the studies included (item 10) as well as the lack of assessment of publication bias (item 15).

# Discussion

In this umbrella review, we report the current research regarding HCQ/CQ in humans, including its efficacy and tolerability in rheumatologic disorders, its safety during pregnancy, and its impact on viral diseases. Overall, our findings suggest that these medications are useful in the treatment of rheumatologic conditions, and their use is associated to adverse events when administered for viral diseases. We believe that our findings are important for the current COVID-19 pandemic.

## HCQ/CQ in rheumatology

The efficacy of HCQ/CQ in rheumatoid arthritis has been confirmed and supported by our study showing an improvement in the number of swollen and tender joints, and in the clinician’s global assessment of the disease. As an additional effect, we found that HCQ/CQ is able to reduce the incidence of type 2 diabetes in patients with rheumatoid arthritis. This effect might be explained by a decrease in insulin clearance and degradation rate, and an increase in the secretion of C-peptide. ([Powrie et al., 1991](#_ENREF_42);[Emami et al., 1998](#_ENREF_13)) Their role should be considered while balancing efficacy and side-effects, even if this study suggests that people randomized to HCQ/CQ were less at risk to be lost at follow-up compared to placebo, implying that HCQ/CQ is a generally well tolerated treatment even in the long term. In general, considering their use in rheumatic diseases, we confirmed their efficacy in reducing CVD risk, probably due to the immunomodulatory and anti-thrombotic effect of these drugs. ([Petri, 2011](#_ENREF_41)) Different mechanisms of action are deemed to be responsible for these effects, namely the reduction of platelet aggregation ([Kinlough-Rathbone, 1975](#_ENREF_34)), the increase in blood fluidity ([Ernst et al., 1984](#_ENREF_14)), and the inhibition of prothrombotic mechanism mediated by antiphospholipid antibodies. ([Espinola et al., 2002](#_ENREF_15)) Its anti-inflammatory action is developed through the reduction of factors such as IL-6 and TNF-α ([Wallace, 1994](#_ENREF_58)), and showed in an animal model a reduction of dyslipidemia and atherosclerosis. ([Shi et al., 2019](#_ENREF_50)) These might explain the impact on the cardiovascular system and arguably represent the reason why its role in COVID-19 was considered initially, since many of the mechanisms involved are shared with SARS-CoV-2 infection. ([Yang et al., 2020](#_ENREF_62))

## HCQ/CQ in pregnancy

HCQ/CQ seem to be safe in pregnancy, as also confirmed by our findings, even if our work found an increase of spontaneous abortion in women taking HCQ/CQ. An increase in the risk of premature delivery and IUGR has been seen; however, these associations are not significant. The increase of spontaneous abortion is more likely to be attributed to the underlying autoimmune diseases rather than drug consumption. ([Bundhun et al., 2017](#_ENREF_7)) In rheumatic diseases HCQ is commonly used during pregnancy ([Birru Talabi and Clowse, 2020](#_ENREF_6)). HCQ is recommended in systemic lupus erythematosus pregnancies to control disease flares and reduce the risk of poor obstetrical outcomes; however more data are needed to support HCQ use during pregnancy in patients with antiphospholipid syndrome. ([Andreoli et al., 2017](#_ENREF_1))

## HCQ/CQ in COVID-19

In this paper we highlight the absence of any evidence supporting the use of HCQ/CQ, notably its broad use to treat viral diseases, while suggesting a higher risk of death when used for treating COVID-19. (Singh et al., 2020) Recently HCQ/CQ was used, alone or in combination with azithromycin, for treating COVID-19 in both hospitals and primary care settings, based on the promising results it had in vitro. ([Yao et al., 2020](#_ENREF_63))However, as today, there is no evidence of efficacy, since the only outcome that could be considered as a proxy (the reduction of viral load) was not statistically significant. As shown in a recent systematic review, in fact, the findings regarding COVID-19 are overall sparse and the few intervention studies available are of poor quality. ([Cortegiani et al., 2020](#_ENREF_10))

Moreover, a recent large observational study ([Geleris et al., 2020](#_ENREF_18)) on 1776 hospitalized consecutive patients, shows that hydroxychloroquine administration does not increase nor decrease the risk of intubation or death in COVID-19.

The administration of HCQ/CQ should be carefully evaluated, as it is known to have several side effects, the most worrisome being cardiovascular (torsade de pointes consequent to QTc-prolongation) and ocular (bulls-eye retinopathy). (Ben-Zvi et al., 2012) Proper dosing of maximum 5 mg/kg/die and regular screening according to risk factors are considered necessary for minimizing the risk of adverse reactions. ([Kim et al., 2017](#_ENREF_33)) The extensive use of HCQ, especially in combination with azithromycin, may increase the risk of QTc-prolonging and eventually torsade de pointes (TdP) and death. ([Javelot et al., 2020](#_ENREF_31)) Many experts consider mandatory the monitoring of QT interval, due to its well-known arrhythmogenic cardiotoxicity ([Haeusler et al., 2018](#_ENREF_21)), and monitoring of electrolytes, particularly in those already on treatment with beta-blockers or calcium channel blockers ([Page et al., 2016](#_ENREF_39)), since hypokalaemia, frequently described in COVID-19, predisposes to cardiac conduction disorders ([Xu et al., 2020](#_ENREF_61)). However only a few clinical studies have analyzed the cardiovascular effects of these drugs. ([Hancox et al., 2013](#_ENREF_22)) In a large cohort of COVID-19 patients treated with chloroquine/hydroxychloroquine with or without azithromycin, no instances of TdP or arrhythmogenic death were reported and although the use of these medications resulted in QT prolongation, clinicians seldomly needed to discontinue therapy. ([Saleh et al., 2020](#_ENREF_45))

However, there’s need for high quality RCT studies to define more precisely its role during this COVID-19 pandemic. Since then, considering the side-effects of which HCQ/CQ may be responsible and the lack of evidence for success in improving the prognosis of patients affected by COVID-19, it may be considered as inappropriate to include HCQ/CQ in the guidelines or in protocols for treatment of COVID-19.

## Limitations

The findings of our work should be interpreted taking into account its limitations. The use of pre-established tools for quality assessment of evidence in both interventional and observational studies, which rely on the data reported in the included meta-analysis, even if individually don’t provide lack of credibility, can cumulatively bring some biases and shortcomings. We used an I2<50% as one of the criteria for class I evidence (convincing) in order to assign the best-evidence grade only to robust associations and without hints of bias. However, I2 estimates can also carry substantial uncertainty, and clinical heterogeneity may be substantial even in the absence of statistical heterogeneity. It is known that meta-analyses have considerable limitations ([Ioannidis, 2016](#_ENREF_28)) and their results depend on the choice of the estimate from each primary study and its representation in the meta-analysis (e.g. in the included meta-analyses, clarity about duration of the studies and the dosage of HCQ/CQ were missing). Moreover, applying the criteria suggested by the AMSTAR 2 for evaluating the quality of meta-analyses, we unfortunately observed the presence of low/critically low rating, highlighting several potential biases. This evidence is mainly driven by missing information in item 2 (protocol published before the meta-analysis), 7 (list of excluded studies), or 15 (publication bias quantitative synthesis was not performed).

## Conclusions

In conclusion, in this umbrella review including 6 meta-analyses and 25 outcomes, we confirmed that HCQ/CQ has an important role in rheumatoid arthritis, being able to reduce joint pain and swelling and incidence of type 2 diabetes. Moreover, when used for autoimmune diseases, it lowers CVD risk. We also found that HCQ/CQ is associated with an increase of spontaneous abortion, though this may be also due to the underlying autoimmune disease more than the pharmacological therapy (Bundhun et al, 2017). When used for treating COVID-19, HCQ/CQ seems associated with a higher risk of death.

These aspects should be taken into consideration before widespread utilization of HCQ, even when pre-clinical results suggest its usefulness, as a therapy for new, and still unknown, viral diseases.

The results of our study, highlighting the lack of evidence and the presence of side effects associated with the use of HCQ/CQ for viral diseases, including COVID-19, indicate the urgent need for Randomised Controlled Trials to determine their eventual appropriateness as a therapy for COVID-19.

**Conflicts of Interest:** All authors have no conflicts of interest.

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