

# Systematic Review and Meta-analysis of the Safety of Chloroquine and Hydroxychloroquine From Randomized Controlled Trials on Malarial and Non-malarial Conditions

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## Research

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# Abstract

**Background:** Despite the expectations regarding the effectiveness of chloroquine (CQ) and hydroxychloroquine (HCQ) for coronavirus disease (COVID-19) management, concerns about their adverse events have remained.

**Objectives:** The objective of this systematic review was to evaluate the safety of CQ and HCQ from malarial and non-malarial randomized clinical trials (RCTs).

**Methods:** The primary outcomes were the frequencies of serious adverse events (SAEs), retinopathy, and cardiac complications. Search strategies were applied to MEDLINE, EMBASE, LILACS, CENTRAL, Scopus, and Trip databases. We used random-effects model to pool results across studies and Peto one-step odds ratio (OR) for event rates below 1 %. Both-armed zero-event studies were excluded from the meta-analyses. We used the Grading of Recommendations Assessment, Development, and Evaluation system to evaluate the certainty of evidence.

**Results:** Ninety-two RCTs were included. We found no significant difference between CQ/HCQ and control (placebo or non-CQ/HCQ) in the frequency of SAEs (OR: 0.98, 95 % confidence interval [CI]: 0.71–1.36, 25 trials, 11,605 participants, moderate certainty of evidence). No clear relationship was observed between CQ/HCQ and retinopathy (OR: 1.63, 95 % CI: -0.4–6.57, 5 trials, 344 participants, very low certainty of evidence). There was a low certainty of evidence of the effect of CQ/HCQ *versus* control on cardiac complications (Relative risk: 1.48, 95 % CI: 1.1–1.98, 8 trials, 5,970 participants).

**Conclusions:** CQ and HCQ might be safe, with low frequency of SAEs on malarial and non-malarial conditions. No clear effect of their use on the incidence of retinopathy and cardiac complications was observed.

The protocol for this systematic review was registered with **PROSPERO** (registration number: CRD42020177818)

## Background

Chloroquine (CQ) and hydroxychloroquine (HCQ) were originally developed for the treatment of malaria; however, several additional drug properties have been discovered, allowing for their use in the treatment of different non-malarial conditions, including rheumatological, dermatological, and immunological diseases [1]. There is also a growing body of evidence to support their therapeutic potential in cancer, chronic kidney disease, and metabolic disorders [1, 2].

The *in vitro* antiviral activity of CQ has been studied for many decades and the growth of different viruses can be inhibited *in vitro* by both CQ and HCQ [3]. Therefore, the effectiveness of these drugs has been studied in relation to a variety of acute infectious diseases, including zika, influenza A H5N1, Ebola,

dengue, and chikungunya, as well as chronic viral infections, including hepatitis C and human immunodeficiency virus [3–5].

The most common adverse events (AEs) of these medications are related to gastrointestinal intolerance, such as vomiting, nausea, diarrhea, and abdominal discomfort [6]. Cutaneous manifestations, such as itching, skin rash, photosensitivity, and hyperpigmentation [7] can also occur. Less frequent adverse effects, such as myopathy, neuromyopathy, and cardiotoxicity can be more severe and irreversible [1].

Cardiac conduction disorders (bundle branch block and atrioventricular block), heart failure, ventricular hypertrophy, hypokinesia, valve dysfunction, pulmonary hypertension, and QT prolongation are effects associated with CQ and HCQ [8].

The major long-term AE associated with these medications is retinopathy, which can cause irreversible visual damage. The risk of development is 1% after 5 years of chronic use, which increases to 2% and 20% when used for more than 10 and 20 years, respectively [9].

Faced with the health crisis triggered by the coronavirus disease (COVID-19) pandemic and the absence of a specific drug therapy so far, CQ and HCQ have been evaluated for their possible effectiveness in the treatment of this disease [10]. Nevertheless, despite the expectations regarding their effectiveness, the concern about their adverse side effects has remained. Some researchers consider that a wide use of the drugs will expose some patients to rare but potentially fatal side effects [11], and those who believe in their potential efficacy justify that these medications have a well-established safety profile.

Therefore, as these drugs have been used for many decades for malarial and non-malarial conditions, we conducted a systematic review of randomized clinical trials (RCTs) to evaluate the safety of CQ/HCQ in different conditions and populations.

## Methods

This systematic review was conducted according to Cochrane Collaboration [12] and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [13]. Its protocol was registered in the International Prospective Register of Systematic Reviews (CRD42020177818).

## Eligibility criteria

We selected RCTs that meet the "PICO" structure described below.

### Participants (P)

An individual, regardless of gender and age, diagnosed with a malarial or non-malarial condition, whose treatment was with either CQ or HCQ.

### Types of Interventions (I)

CQ or HCQ

## **Comparison (C)**

The comparison group was placebo or no CQ/HCQ. Intervention and comparison groups must have received the same standard treatments for patient's basal disease.

## **Outcomes (O)**

The primary outcomes were the number of patients with serious adverse events (SAEs), the number of patients with retinopathy, and the number of patients with cardiac complications.

We considered any AE or suspected adverse reaction that resulted in any of the following outcomes as SAE: death, a life-threatening AE, hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity, substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect [14].

We considered retinopathy diagnosed after the use of CQ/HCQ in patients who previously had normal baseline ophthalmologic examination results as CQ/HCQ-induced retinopathy. We considered conduction disorders and other non-specific adverse cardiac events (ventricular hypertrophy, hypokinesia, heart failure, pulmonary arterial hypertension, and valvular dysfunction) as cardiac AE with probable association with CQ or HCQ [8].

The secondary outcomes were the total number of participants with any CQ- or HCQ-related AE, number of withdrawals due to CQ- or HCQ-related AE, number of patients with gastrointestinal AEs (nausea, vomiting, stomach ache, diarrhea, loss of appetite, and weight loss) [1], number of patients with cutaneous manifestations (skin rash, itching, hair loss, erythroderma, exfoliative dermatitis, urticaria, eczematous eruptions, photosensitivity, and erythema annulare centrifugum) [1], number of patients with myopathy, number of patients with visual symptoms, and number of patients with auditory symptoms.

## **Time of outcome evaluation**

The outcomes were evaluated at 4 weeks and after 4 weeks. Trials with outcomes within these time-points were combined with the closest time-point.

## **Exclusion criteria**

We excluded non-RCTs as well as studies where intervention and comparison groups received different standard treatments for patient's basal disease.

## **Identification of studies**

## **Electronic databases**

General research strategies were applied to the main electronic health databases: Embase (Elsevier, 1980–2020), Medline (PubMed, 1966-20-April-2020), LILACS (Virtual Health Library, 1982- 20-April-2020),

Controlled Clinical Trials of Cochrane Collaboration (CENTRAL – Cochrane 20-April-2020), Trip database, SCOPUS, and Web of Science (20-April-2020). The search strategies contained index terms and synonyms of chloroquine and hydroxychloroquine. On PubMed, we used the filter for RCT, as supported by Cochrane, and the embedded filter was used for the same purpose on Embase. The search strategy for each database is included in the supplementary file. As a huge number of studies met our eligibility criteria, the search for unpublished source (clinical study report, trial registers, and regulatory agency websites) will be performed in a near future.

EndNote X9 citation management software was used to download references and remove duplicate entries. The initial screening of abstracts and titles was performed using the free web application Rayyan QCRI [15].

## **Study selection**

Two reviewers (MSB and VSNN) independently selected potentially eligible studies for inclusion in the review based on the titles and abstracts. The studies selected for full-text review were subsequently assessed for adequacy to the proposed 'PICO' structure. In case of disagreement, there was a consensus meeting between the reviewers for a final decision.

## **Data extraction and management**

The two reviewers (MSB and VSNN) used a standard form to extract the following data from the selected studies: year of publication, country, pragmatic or non-pragmatic RCT, basal disorder, population group (children, adults, and pregnant women), sample size, follow-up time, type of intervention and comparison, daily dosage of the intervention, number of patients randomized to intervention and comparison group, number of patients in each group with the primary and secondary outcomes, and mean age of participants.

For a specific outcome, we only extracted data as 'zero' if it was clearly listed as such in the study report; otherwise, we interpreted that the authors did not evaluate this outcome.

To ensure consistency between reviewers, we performed a calibration exercise before beginning the review. In the case of duplicate publications or multiple reports from the primary study, data extraction was optimized using the best information available for all items in the same study.

## **Assessment of risk of bias in included studies**

For the primary outcomes from each selected trial, the risk of bias was assessed according to the revised Cochrane risk-of-bias tool for RCTs (RoB 2 tool) [16], which considered five domains for each outcome evaluated. The domains were (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, (5) bias in selection of the reported result. Each of the items was evaluated in pairs and independently by 14 reviewers as having 'low risk of bias', 'some concerns', or 'high risk of bias'. We classified SAEs as outcome available for all or nearly all participants, with less than 5% loss to follow-up.

For studies in which such losses were higher than 5%, we considered a low risk of bias in this domain if the rates were balanced between groups, the causes were justified, and not related with any SAE. For outcomes where assessors were aware of the intervention received by study participants, we considered that the assessment of the retinopathy and cardiac complications could have been influenced by the knowledge of the intervention received, but not for SAE. For cardiac complications in studies where there was no information that all participants were subjected to the same method and frequency of investigation, we considered that the measurement or ascertainment of the outcomes differed between the groups, and this domain was classified as high risk of bias.

## Unit of analysis

The unit of analysis was the data published in the studies included. We used the data available in published articles, and we preferentially used data from intention-to-treat analysis. For the studies that did not provide an intention to treat analysis, we considered the number of patients randomized in each group, and for patients who missed the follow up, we input as absent the AE evaluated [17].

## Data analyses

Similar outcomes were plotted in the meta-analysis using the Stata Statistical Software 16 (*Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC). The relative risk (RR) was calculated with a 95% confidence interval (CI) as an effect size of CQ/HCQ, and a random-effect model was used for the meta-analysis. However, as this systematic review involved safety measures, and to avoid underestimating the harm, we used Peto one-step odds ratio (OR) method for event rates below 1% [12] [18]. In this situation, both-armed zero-event (BAOE) studies were excluded from the meta-analysis.

## Sensitivity analysis

For SAE, we performed sensitivity analysis to evaluate 'high risk', 'some concerns', and 'low risk' of bias according to Rob 2, placebo or non-CQ/HCQ as the comparison group, sample size ( $\geq 100$  participants *versus*  $< 100$  participants), and per protocol.

## Subgroup analysis

For SAE, we performed subgroup analyses according to the type of intervention (CQ or HCQ), patient diagnosis, type of population (children, adults, and pregnant women), daily dosage (less than 500 mg *versus*  $>$  than 500 mg for CQ,  $<$  than 400 mg *versus* more than 400 mg for HCQ), time of follow up (up to 4 weeks *versus* after 4 weeks). We used the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN tool) to assess the credibility of the subgroups [19].

## Heterogeneity assessment

Inconsistencies between the results of the studies included were ascertained by visual inspection of forest plots (no overlap of CIs around the effect estimates of the individual studies) and by Higgins or  $I^2$  statistic, in which  $I^2 > 50\%$  indicated a moderate probability of heterogeneity, and by chi-squared tests ( $\text{Chi}^2$ ), where  $p < 0.10$  indicated heterogeneity.

# Quality of evidence

The quality of the evidence of the effect size was assessed according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines [20].

## Results

The search strategies yielded different studies, and after removing duplicates, 6277 studies remained. We selected 188 studies that had a high probability of meeting our inclusion criteria for a complete examination (Fig. 1). After completely examining these references, 92 studies met our eligibility criteria and therefore were included in this review.

A total of 96 studies were excluded for the following reasons: no AE was evaluated ( $n = 38$ ), no control group as placebo or non-comparator for CQ or HCQ ( $n = 7$ ), non-RCT ( $n = 4$ ), no report of the outcomes per group studied ( $n = 6$ ) (Supplementary file), studies are still ongoing ( $n = 25$ ) (Supplementary file), and unevaluated eligibility criteria ( $n = 16$ ) (Supplementary file).

## Study Characteristics

Out of 92 studies included, eight were on COVID-19 [21–28], 13 studies were on malaria [29–41], 11 on other infectious conditions [42–53], 31 were on rheumatology [54–84], four on dermatologic diseases [85–88], eight on cancer [89–96], five were on metabolic disease [97–101], and the remaining were on other conditions [102–112]. Fifty-seven studies used HCQ (11,274 participants) as intervention and 35 used CQ (6,997 participants). Most studies used placebo as comparator, seven studies were on children [29, 30, 32, 35, 92, 38, 56], two on pregnant women [76, 41], and the others were on adult population. Most studies used daily intervention dose  $\geq$  than 500 mg for CQ and  $\geq$  than 400 mg for HCQ.

In most of the included studies, the participants had chronic conditions, and, consequently, the intervention and follow up were beyond 4 weeks. Meanwhile, the total sample size was higher in studies on acute conditions, with follow up less than 4 weeks. Table 2 (supplementary file) presents descriptive data of all the studies included.

## Risk of bias

Figure 2 shows the risk of bias corresponding to the included studies for the SAE outcome, and Fig. XVIII and Fig. XIX in the supplementary file, respectively, present the risk of bias for retinopathy and cardiac complications.

## Meta-analysis

Regarding primary outcomes, there is no evidence to support the difference between CQ/HCQ and control group (placebo or non-CQ/HCQ) with regard to the frequency of SAE (OR: 0.98, 95% CI: 0.71–1.36, 25



studies, 11,605 participants, moderate certainty of evidence, Table 1, Fig. 3). Forty-five BAOE studies with 4,503 participants were excluded from this analysis (Fig. 3).

Table 1

Summary of findings according to GRADE approach. CQ/HCQ compared to Placebo or no CQ/HCQ for malarial and non-malarial conditions.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (Number of studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Non CQ/HCQ	Risk with CQ/HCQ				
SAE	12 per 1.000	<b>12 per 1.000</b> (8–16)	<b>OR 0.98</b> (0.71–1.36)	11605 (25 RCTs)	⊕⊕⊕● MODERATE <sup>a</sup>	CQ/HCQ likely does not increase SAE.
Retinopathy	18 per 1.000	<b>28 per 1.000</b> (7–105)	<b>OR 1.63</b> (0.40–6.57)	344 (5 RCTs)	⊕●●● VERY LOW <sup>b,c</sup>	The evidence is very uncertain about the effect of CQ/HCQ on retinopathy.
Cardiac complications	26 per 1.000	<b>39 per 1.000</b> (29–52)	<b>RR 1.48</b> (1.10–1.98)	5970 (8 RCTs)	⊕⊕●● LOW <sup>d</sup>	CQ/HCQ may result in a slight increase in cardiac complications.
<p>*<b>The risk in the intervention group</b> (and its 95% confidence interval) is based on the assumed risk in the comparison group and the <b>relative effect</b> of the intervention (and its 95% CI).</p> <p>CI: Confidence interval; OR: Odds ratio; RR: Risk ratio; SAE: Serious adverse events; CQ: Chloroquine; HCQ: Hydroxychloroquine; GRADE: Grading of Recommendations Assessment, Development, and Evaluation</p>						
<b>GRADE levels of evidence</b>						
<b>High certainty:</b> We are very confident that the true effect lies close to that of the estimate of the effect						
<b>Moderate certainty:</b> 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						
<b>Low certainty:</b> Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect						
<b>Very low certainty:</b> We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect						
<i>Explanations</i>						
a. The quality of evidence was rated down due to non-inclusion of unpublished data.						
b. According to RoB 2, the studies included were classified as 'some concerns' or 'high risk' of bias due to the following reasons: missing data, no mention of the method used to measure retinopathy, and no information regarding allocation concealment.						

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (Number of studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Non CQ/HCQ	Risk with CQ/HCQ				
c. Wide confidence interval. Considering a prevalence of 7.8% of retinopathy in non-diabetic population (Klein,1992), and a 1% of retinopathy risk in the first 5 years of HCQ treatment ( Petri 2020), the minimum sample size required for the detection of this outcome is 4533 (level of significance = 5%; power (1- β) = 80%). The optimal information size criterion was not met, and the quality of evidence was rated down by two levels for imprecision						
d. According to RoB 2, most of the studies included were classified as high risk of bias due to the following reasons: missing data, no mention of the method used to measure cardiac arrhythmia, and no information on if the participants of both groups were subjected to same method and frequency of outcome evaluation						

Regarding the association between CQ/HCQ and the frequency of retinopathy, the evaluation of the risk of bias (most studies did not mention the method used to evaluate this outcome) and imprecision (wide confidence interval, no achievement of optimal information size) did not indicate any clear effect (OR: 1,63, 95% CI -0.4–6.57, 5 studies, 344 participants, very low certainty of evidence, Fig. 4, Table 1). Twenty BAOE studies with 1,559 participants were excluded from this analysis (Fig. 4).

CQ/HCQ may have a small effect on cardiac complications; however, due to missing data and the concern that participants were not subjected to the same method of investigation, the certainty of evidence was low (RR:1.48, 95% CI: 1.1 to 1.98, 8 trials, 5,970 participants, Fig. 5, Table 1). Four BAOE studies with 879 participants were excluded from this analysis (Fig. 3). The complications reported were cardiac arrhythmia and prolongation of QTc interval. Two studies reported these complications as SAE (a prolonged QT interval with ventricular arrhythmias, and a case of torsades de pointes) (26)[71]. Two studies were on pharmacokinetic analysis, and all participants performed serial electrocardiograms [40, 37]. Two studies were on COVID-19, and the screening method for the complication was not mentioned. However, one of the studies stated that fewer serial electrocardiograms were performed for patients in the control group than for patients in the HCQ group [22].

For the secondary outcomes, the administration of CQ/HCQ increases the incidence of total AE (RR 1.39, 95% CI: 1.19–1.62, 45 studies, 9,428 participants, supplementary file), nausea/vomiting (RR 1.89 95% CI: 1.48–2.42, 22 studies, 6096 participants, supplementary file), diarrhea (RR 1.64, 95% CI: 1.15–2.36, 19 studies, 5,239 participants, supplementary file), withdrawal due to AE (RR 1.38, 95% CI: 1.11–1.72, 50 studies, 7,760 participants, supplementary file), headache (RR 1.56, 95% CI: 1.11–2.2, 22 studies, 6,131 participants, supplementary file), and dermatological affections (RR 1.61, 95% CI: 1.1–2.33, 16 studies, 3,682 participants, supplementary file). There was no clear evidence to support a difference between the CQ/HCQ and control group with regard to visual and auditory symptoms (RR 1.5, 95% CI: 0.88 to 2.53, 26 studies, 6,6758 participants; RR 1.64, 95% CI: 0.94 to 2.79, 10 studies, 4,687 participants, respectively,

supplementary file). Only two studies reported myopathy as AE, and no difference was found between the groups.

For SAE, although more than ten studies were included in the meta-analysis, we could not evaluate publication bias by funnel plot or Egger test because all the studies showed no statistically significant difference between groups (CQ/HCQ *versus* placebo or non-CQ/HCQ). Nevertheless, the quality of evidence in this domain was rated down due to the non-inclusion of unpublished data.

The subgroup analysis according to type of intervention, patient diagnosis, type of population, daily dosage, and time of follow up did not indicate that CQ/HCQ increased the frequency of SAE (supplementary file). However, for the subgroup analysis of studies (not for subsets of participants), with 3–4 studies in the smallest subgroup, all the effect modification analyses were classified as having low credibility.

In the sensitivity analyses (according to overall risk of bias, placebo or non-CQ/HCQ, sample size), a 'no true' CQ/HCQ effect on SAE was observed (supplementary file).

## Discussion

Considering the promising action of CQ and HCQ in the treatment of COVID-19 at the beginning of the pandemic, many guidelines started to include them in the management of this condition. Consequently, a significant number of patients used these medications, and a great concern emerged regarding their safety. Thus, we conducted a systematic review of RCTs to evaluate the safety of CQ/HCQ in different conditions and populations.

We chose, as our primary outcomes, the frequency of rare but potentially fatal AEs: SAEs, retinopathy, and cardiac complications. The study included 92 RCTs, with a total of 18,177 participants. With moderate certainty, we did not find evidence that either CQ or HCQ, compared with placebo or non-CQ/HCO, increased the frequency of SAEs. Moreover, due to imprecision and risk of bias, we did not observe any clear effect of CQ/HCQ on retinopathy. Although the meta-analysis showed that CQ/HCQ increased the incidence of cardiac complications, the certainty of evidence was low. This is because the outcomes of the trials that contributed mostly to this analysis were assessed by the site investigators, who were aware of the trial-group assignments. Therefore, we were concerned that HCQ groups have been more investigated for cardiac complications than comparison groups, as stated Cavalcanti et al. [22].

Although the literature has reported several CQ/HCQ-associated AEs, both drugs are generally considered safe [113]. A systematic review of cardiac complications attributed to these medications identified 86 cases/series providing information on 127 participants with AE probably caused by CQ/HCQ. Majority of the patients were treated with CQ and most had been treated for a long time (median, 7 years; minimum, 3 days; maximum, 35 years), with high cumulative doses (median, 1235 g and 803 g for hydroxychloroquine and chloroquine, respectively). Conduction disorders were the main AE reported, affecting 85% of the patients. Moreover, the authors highlighted that cases/series do not allow for an

association of causality, and the risk of cardiac complications attributed to CQ/HCQ could not be quantified [8].

While this review was being performed, two unregistered systematic reviews were published on the same subject. Ren et al. identified RCTs that compared the safety profiles of CQ or HCQ with placebo or other active treatment. Their study included 40 studies, with 2,137 participants and 1,096 participants in the CQ and HCQ trials, respectively. They used RR as effect size, and they concluded that the overall mild or total AEs were statistically higher with CQ or HCQ than with placebo. From the meta-analysis of SAEs, the RR values for CQ and HCQ were 1.1 (95% CI: 0.41 to 2.9, six studies) and 1.12 (95% CI: 0.58 to 2.15, 14 trials), respectively [114]. Eljaaly et al. searched PubMed and EMBASE databases for RCTs of adults comparing AE of HCQ with placebo for any indication. Nine RCTs with a total of 916 patients were included. Cardiac toxicity was not reported, and the meta-analysis found a significantly higher risk of skin pigmentation in HCQ users than in those that received placebo. However, the study did not evaluate the frequency of SAE and retinopathy [115].

Our review included more studies and consequently more participants than the two published reviews. Both reviews included only studies with placebo and the latter included only the studies on HCQ. We did not exclude non-placebo-controlled studies in the evaluation of SAE because we did not believe that the lack of blinding in the outcome assessment, as well as in the intervention received, could cause performance or detection bias. Additionally, we performed a sensitivity analysis separating placebo trials from the trials with non-CQ/HCQ, and for each subgroup analysis, there was no difference in the frequency of SAE, and the CIs were the same (supplementary file).

Our systematic review had some limitations. The most significant was that there was no search for unpublished sources of data on AE. This includes clinical study reports, trial registers, and regulatory agency websites [12]. There is strong evidence that much of the information on AE are unpublished and that the number and range of AE are higher in unpublished than in published versions of the same study [116]. Golder and colleagues found that the median percentage of published documents with AE information was 46% compared with 95% in the corresponding unpublished documents [116]. Because of this, we rated down the quality of evidence by one level for publication bias. Additionally, the search for SAE, retinopathy, and cardiac complications related to CQ/HCQ from unpublished data will be the next step of this project. The second limitation was the number of BAOE studies that were excluded from the meta-analysis of primary outcomes. As these studies do not provide any indication of direction or magnitude of the relative treatment effect, they are naturally excluded in meta-analysis of OR and RR [12]. However, there is no consensus on whether studies with no observed events in the treatment and control arms should be included or not in a meta-analysis of RCTs. Cheng and collaborators simulated 2500 data sets for rare event outcome with different scenarios by varying the baseline event rate, treatment effect and number of patients in each trial, and between-study variance [18]. In accordance with another study [117], they concluded that the Peto one-step odds ratio method is the least biased and most powerful method for the meta-analyses of rare events [12]. Additionally, including BAOE studies for AE can underestimate possible harmful side effects, which could expose patients to unnecessary danger. Thus,

they recommended that for the analysis of rare AEs, Peto method should be adopted in conjunction with the exclusion of BAOE studies from analysis. The third limitation was that most of the trials included were not pragmatic studies, and individuals with risk factors for AEs related to CQ/HCQ were excluded. This means that the safety profile of CQ/HCQ presented here was not designed to the real-world, and it could be underestimating harm.

## Conclusion

In conclusion, from the findings of this systematic review, CQ and HCQ seem to be safe, with low frequency of SAE from RCTs on malarial and non-malarial conditions. Due to imprecision and bias in measurement of the outcomes, no clear effects of their use on the incidence of retinopathy and cardiac complications were observed.

## Abbreviations

AE	Adverse event
BAOE	Both-armed zero-event
CI	Confidence interval
CQ	Chloroquine
HCQ	Hydroxychloroquine
OR	Odds ratio
RCT	Randomized controlled trial
RR	Relative risk
SAE	Serious adverse events

## Declarations

### Ethics approval and consent to participate

As no primary data collection was carried out, no formal ethical assessment was required by our institution.

## Consent of publication

Non applicable.

## Availability of data and material

All data generated or analyzed for this systematic review are included in this published article (and its supplementary file).

## Competing interests

The authors have no conflicts of interest to declare.

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## Authors' contributions

VSNN and LT conceptualized and design the study. VSNN developed the search strategies. VSNN and MSB independently screened eligible studies and extracted data from included studies. VSNN, MSB, FB, RGOFL, MSFL, LRB, LTS, TOFO, ASM, FRKO, LPFA, JFA, RAMBA, and JSCG assessed in pairs and independently the risk of bias. VSNN, LT, and MSB performed the meta-analysis. VSNN supervised all the phases of this review and refereed any disagreement to avoid errors. All authors participated in data synthesis and in the assessment of quality of evidence. All authors critically revised the manuscript and approved its final version.

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## Figures

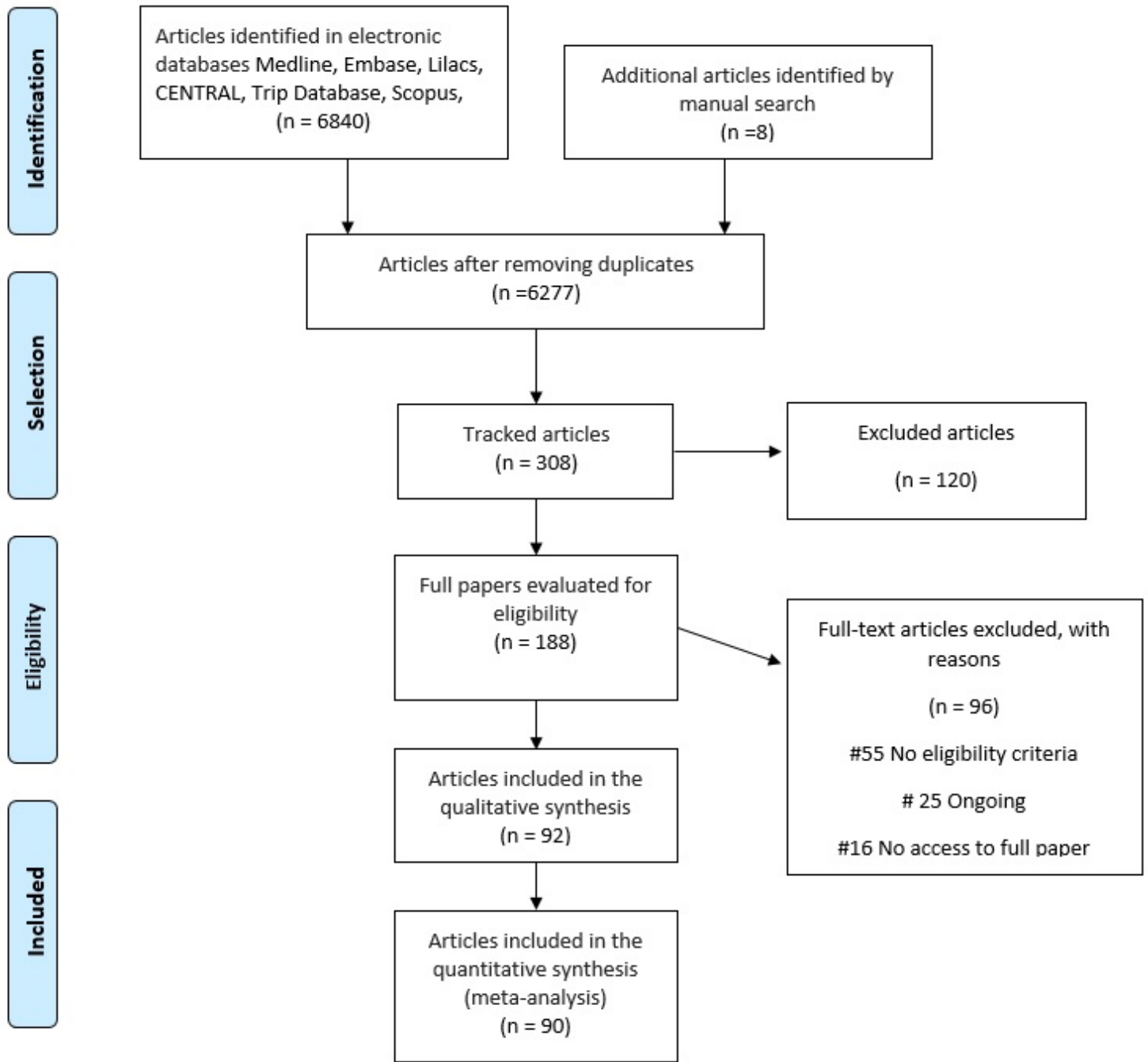


Figure 1

Flow diagram of selected studies

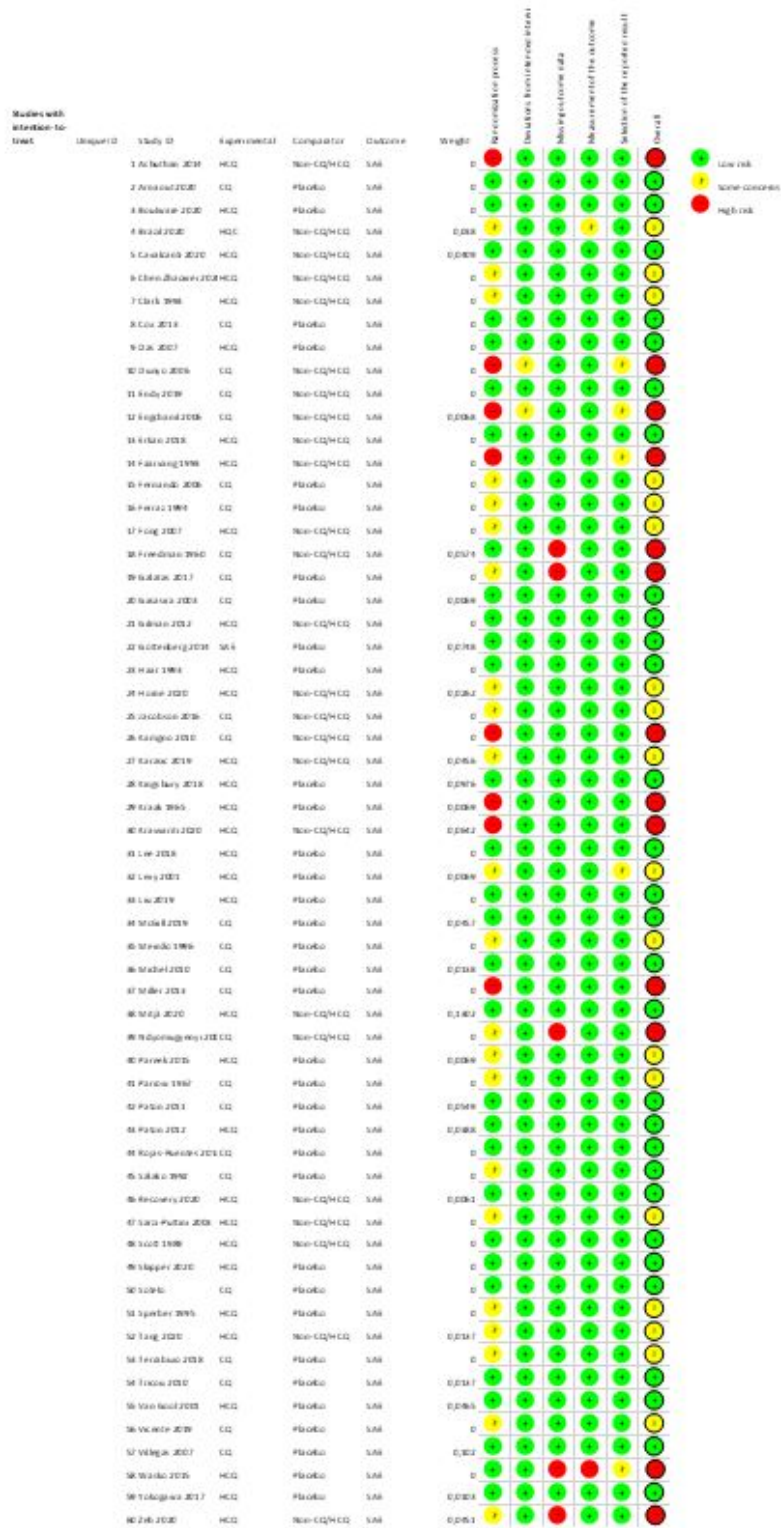


Figure 2

Risk of bias according to RoB 2 for serious adverse events (SAE).

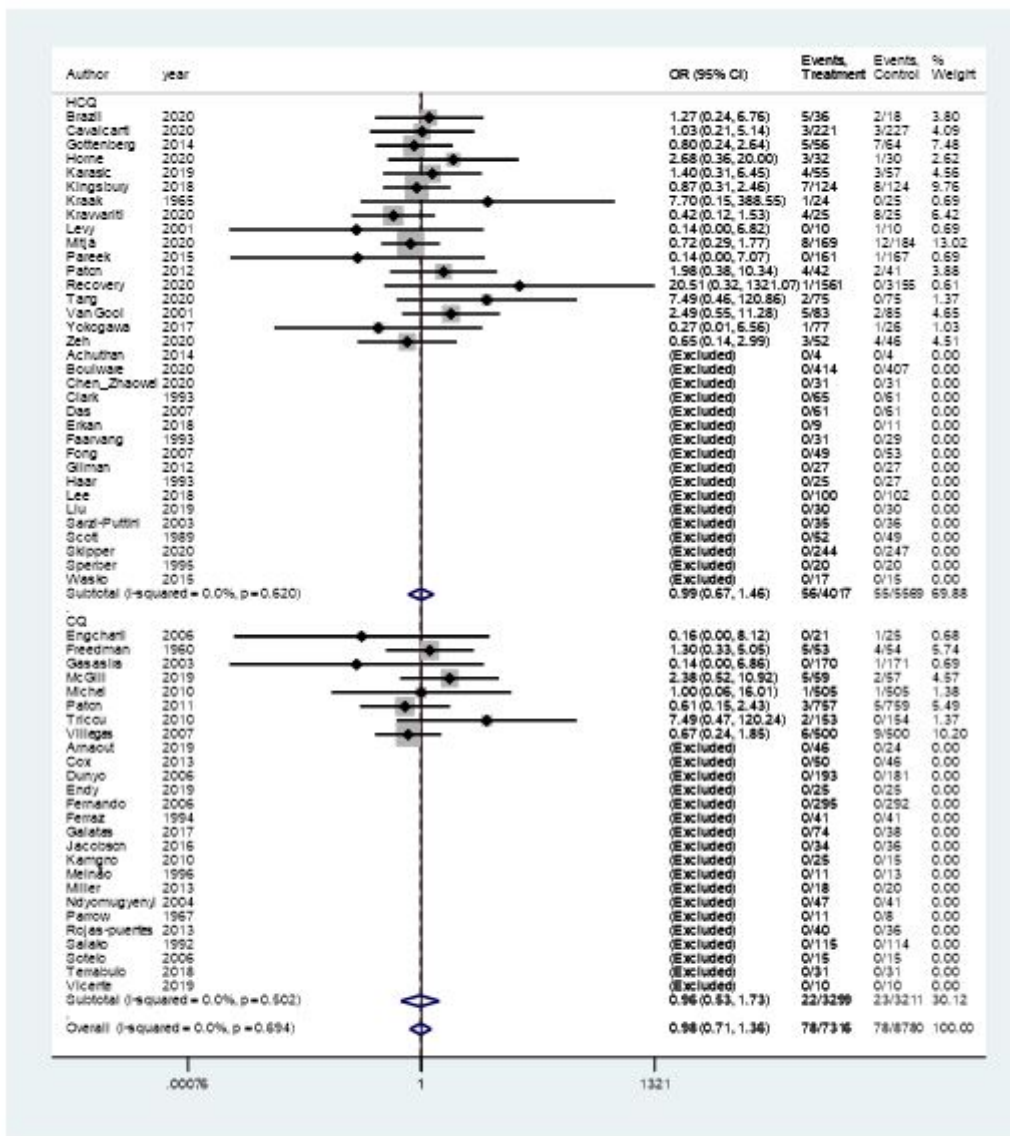


Figure 3

Meta-analysis for frequency of serious adverse events. Subgroup analysis according to type of intervention. CQ: Chloroquine, HCQ: Hydroxychloroquine. Peto method was adopted and studies with both-armed zero-event were excluded from the analysis.

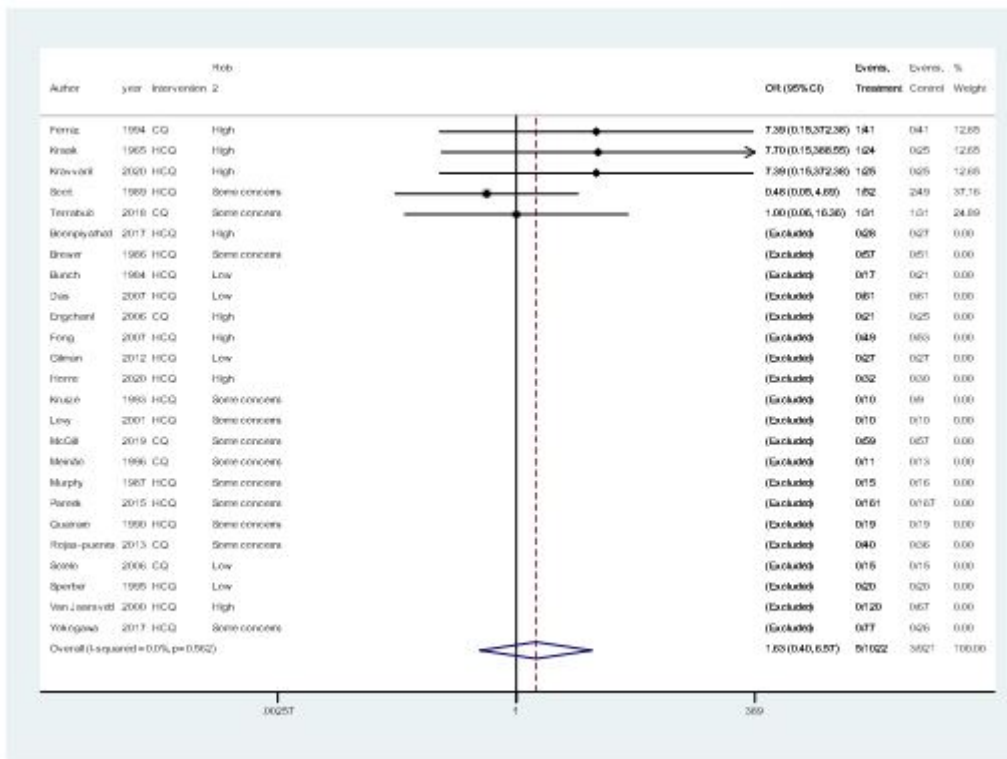


Figure 4

Meta-analysis for frequency of retinopathy. Subgroup analysis according to type of intervention. CQ: Chloroquine, HCO: Hydroxychloroquine. Peto method was adopted and studies with both-armed zero-event were excluded from the analysis.

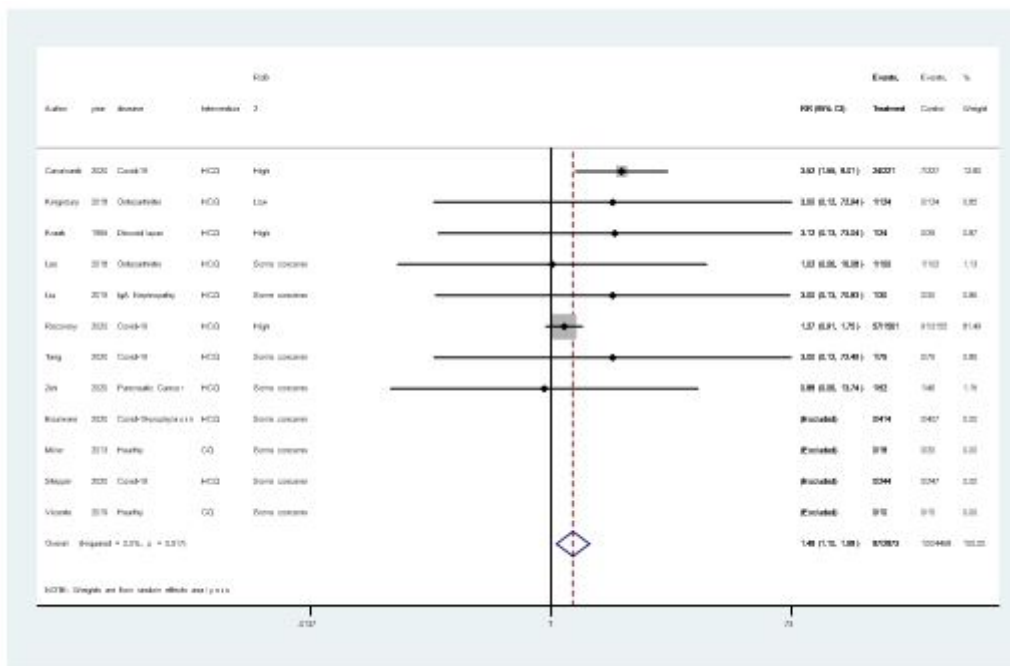


Figure 5

Meta-analysis for frequency of cardiac complications. Studies with both-armed zero-event were excluded from the analysis.

## Supplementary Files

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