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Revisão Sistemática e Meta-Análise de Ensaio Clínicos
Randomizados da Segurança da Cloroquina e da
Hidroxicloroquina na COVID-19 e em Outras Condições

Tese apresentada à Faculdade de
Medicina, Universidade Estadual Paulista
“Júlio de Mesquita Filho”, Câmpus de
Botucatu, para obtenção do título de
Doutora em Fisiopatologia em Clínica
Médica.

Orientadora: Profa. Dra. Vânia dos Santos Nunes Nogueira

Botucatu
2024

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Palavras-chave: COVID-19; Cloroquina; Efeitos adversos; Hidroxicloroquina; Revisão sistemática.

ATA DA DEFESA PÚBLICA DA TESE DE DOUTORADO DE MAYRA SOUZA BOTELHO, DISCENTE DO PROGRAMA DE PÓS-GRADUAÇÃO EM FISIOPATOLOGIA EM CLÍNICA MÉDICA, DA FACULDADE DE MEDICINA - CÂMPUS DE BOTUCATU.

Aos 17 dias do mês de abril do ano de 2024, às 14:00 horas, por meio de Videoconferência, realizou-se a defesa de TESE DE DOUTORADO de MAYRA SOUZA BOTELHO, intitulada **Revisão Sistemática e Meta-Análise de Ensaaios Clínicos Randomizados da Segurança da Cloroquina e da Hidroxicloroquina na COVID-19 e em Outras Condições**. A Comissão Examinadora foi constituída pelos seguintes membros: Profa. Dra. VANIA DOS SANTOS NUNES NOGUEIRA (Orientador(a) - Participação Virtual) do(a) Depto. de Clínica Médica / FM/Botucatu - Unesp, Profa. Dra. SARAH NASCIMENTO SILVA (Participação Virtual) do(a) Pesquisa Clínica e Políticas Públicas em Doenças Infecto-Parasitárias / Fiocruz - Instituto René Rachou, Profa. Dra. DANIELA FERNANDA DOS SANTOS ALVES (Participação Virtual) do(a) Faculdade de Enfermagem / Universidade Estadual de Campinas. Após a exposição pela doutoranda e arguição pelos membros da Comissão Examinadora que participaram do ato, de forma presencial e/ou virtual, a discente recebeu o conceito final: Aprovada. Nada mais havendo, foi lavrada a presente ata, que após lida e aprovada, foi assinada pelo(a) Presidente(a) da Comissão Examinadora.

Profa. Dra. VANIA DOS SANTOS NUNES NOGUEIRA

Impacto potencial desta pesquisa

O impacto científico esperado desta pesquisa “Revisão Sistemática e Meta-Análise de Ensaio Clínico Randomizado da Segurança da Cloroquina e da Hidroxicloroquina na COVID-19 e em Outras Condições” envolve diversas áreas da saúde. Primeiramente, a nossa revisão trouxe informações valiosas sobre a segurança da cloroquina (CQ) e hidroxicloroquina (HCQ) no contexto da pandemia de COVID-19, momento no qual essas drogas foram amplamente utilizadas, sem um perfil de segurança estabelecido para essa condição. A revisão foi publicada em 2021 com seus principais resultados.

Em segundo lugar, a revisão também fornece uma síntese da evidência quanto à segurança da HCQ no tratamento de doenças reumatológicas, para as quais ainda possui relevância terapêutica. Além disso, nossos resultados apontam para a necessidade da comunidade científica de reportar eventos adversos de forma mais adequada nos ensaios clínicos randomizados, com o intuito de aprimorar a avaliação da segurança das intervenções na literatura.

Em relação ao impacto social, a pandemia da COVID-19 foi um momento único, quando as evidências científicas passaram a ter uma importância direta e perceptível nas tomadas de decisão que envolviam a sociedade. Nesse sentido, uma revisão que aborda a segurança de medicações que passaram a ter uso indiscriminado, em certos casos até sem indicação médica, pode ter um papel fundamental no esclarecimento da população. CQ e HCQ não se mostraram eficazes para tratamento da COVID-19 e, apesar disso, muitos indivíduos ainda faziam uso com esse intuito, a despeito de possíveis eventos adversos. A nossa revisão mostrou, por exemplo, que CQ e HCQ podem aumentar complicações cardíacas em pacientes com COVID-19.

Em contrapartida, a nossa revisão não mostrou aumento de eventos adversos sérios ou complicações cardíacas nos estudos envolvendo doenças reumatológicas. Alguns indivíduos com indicação do uso de HCQ por doenças reumatológicas, passaram a questionar seus médicos ou até suspenderam o uso de suas medicações durante a pandemia. Nesse caso, a evidência científica pode ter papel direto no esclarecimento da população para que mantenha sua qualidade de vida e seus tratamentos já instituídos.

Potential Impact of this Research

The expected scientific impact of this research “Systematic Review and Metaanalysis of the Safety of Chloroquine and Hydroxychloroquine from Randomized Controlled Trials on COVID-19 and Other Conditions” involves several areas of medicine. Firstly, in the context of the COVID-19 pandemic, our review provided valuable information about the safety of chloroquine (CQ) and hydroxychloroquine (HCQ), which were widely used without an established safety profile for this condition. The review was published in 2021 with its main results.

Secondly, the review also provides a synthesis of evidence regarding the safety of these medications, which still holds relevance in the treatment of rheumatological diseases. Additionally, our results point to the need for the scientific community to report adverse events more appropriately in randomized clinical trials, which can improve the assessment of safety in the literature.

Regarding the social impact, the COVID-19 pandemic was a unique moment, when scientific evidence became directly and noticeably important in societal decision-making. In this sense, a review addressing the safety of medications that were often being used indiscriminately can play a fundamental role in educating the population. CQ and HCQ were not found to be effective in treating COVID-19, yet many individuals continued to use them for this purpose, despite potential adverse events. Our review showed, for example, that CQ and HCQ may increase cardiac complications in COVID-19 patients.

In contrast, our review did not show an increase in serious adverse events and cardiac complications in studies of rheumatological diseases. Some individuals who were prescribed HCQ for rheumatological conditions questioned their doctors or even discontinued the use of their medications due to concerns arising from misinformation. In this case, scientific evidence can play a direct role in educating the public to maintain their quality of life with their established treatments.

Dedico este trabalho a Paulo Faria Botelho, Clovis da Silva Souza, Solange Botelho Borges e Natália Evelin de Miranda Meneses (*in memoriam*), avós e tias amorosos que me inspiram.

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Introdução: Diante das especulações quanto à eficácia da cloroquina (CQ) e da hidroxicloroquina (HCQ) para o manejo da COVID-19, surgiram incertezas quanto à real segurança dessas drogas na prática clínica. **Objetivos:** Os objetivos desta revisão sistemática foram avaliar a segurança da CQ e da HCQ a partir dos dados publicados e não publicados de ensaios clínicos randomizados (ECR) de indivíduos com COVID-19 ou outra condição clínica para qual essas medicações foram prescritas e avaliar a qualidade do relato dos eventos adversos (EA) reportados nos estudos incluídos. **Métodos:** Os desfechos primários foram as frequências de eventos adversos graves (EAGs), retinopatia e complicações cardíacas. As estratégias de busca foram aplicadas nas bases de dados MEDLINE, EMBASE, LILACS, CENTRAL, Scopus e *Trip database*. A pesquisa dos estudos não publicados foi realizada no *Google Scholar*, *Web of Science* CPCI-S, repositórios de teses e dissertações e sites de agências reguladoras. Foi utilizado um modelo de efeitos aleatórios para agrupar os resultados entre os estudos e o método de Peto para taxas de eventos abaixo de 1%. Estudos em que não houve eventos em ambos os braços, foram excluídos das meta-análises. A qualidade da evidência foi gerada de acordo com o sistema *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE). A avaliação da qualidade do relato dos EA reportados teve como base os 10 itens da extensão do *Consolidated Standards Reporting Trials* (CONSORT). **Resultados:** Cento e seis ECRs foram incluídos. Não foi encontrada diferença significativa entre CQ/HCQ e controle (placebo ou não-CQ/HCQ) na frequência de EAGs (OR: 0,98, intervalo de confiança de 95% [IC]: 0,76–1,26, 33 estudos, 15.942 participantes, certeza moderada da evidência). No entanto, houve uma certeza moderada de evidência de que CQ/HCQ aumentam a incidência de complicações cardíacas (RR: 1,62, IC 95%: 1,10–2,38, 16 estudos, 9908 participantes). Não foi possível observar clara relação entre o uso de CQ/HCQ e retinopatia (OR: 1,63, IC 95%: - 0,4–6,57, 5 estudos, 344 participantes, certeza de evidência muito baixa). Apenas um estudo não publicado preencheu os critérios de elegibilidade, no qual não houve relato de EAGs, retinopatia ou complicações cardíacas. Quatro das recomendações da extensão do CONSORT não foram adequadamente reportadas pela maioria dos estudos avaliados em COVID-19. **Conclusões:** CQ e HCQ provavelmente não aumentam EAGs, com baixa frequência desses eventos adversos nas condições avaliadas. No entanto, CQ e HCQ podem aumentar as complicações cardíacas, especialmente em pacientes com COVID-19. Não há efeito claro sobre o uso da CQ/HCQ quanto a incidência de

retinopatia. É necessário reportar adequadamente os eventos adversos em ECRs para que haja uma avaliação mais precisa desses desfechos.

Palavras-chave: Cloroquina, Hidroxicloroquina, COVID-19, Efeitos adversos, Segurança, Revisão sistemática

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 published and unpublished randomized clinical trials (RCTs) in COVID-19 and other conditions. Additionally, the review aimed to assess the quality of adverse event (AE) reported in the included COVID-19 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. The search for unpublished studies was carried out on Google Scholar, Web of Science CPCI-S, theses and dissertation repositories and regulatory agency websites. We used a random-effects model to pool results across studies and Peto's 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 (GRADE) system to evaluate the certainty of evidence. The assessment of the quality of AE reporting was based on the 10 items of the Consolidated Standards of Reporting Trials (CONSORT) extension. **Results:** One hundred and six 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]: 0.76–1.26, 33 trials, 15,942 participants, moderate certainty of evidence). However, there was a moderate certainty of evidence that CQ/HCQ increases the incidence of cardiac complications (RR: 1.62, 95% CI: 1.10–2.38, 16 trials, 9908 participants). 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). One unpublished study met the eligibility criteria, in which there was no report of SAEs, retinopathy or cardiac complications. Four of the CONSORT extension recommendations were not adequately reported by the majority of studies evaluated. **Conclusions:** CQ and HCQ probably do not increase SAEs, with low frequency of these adverse events in the assessed conditions. However, they may increase cardiac complications especially in patients with COVID-19. No clear effect of their use on the incidence of retinopathy was observed. It is necessary to adequately report adverse events in randomized controlled trials (RCTs) to conduct a more accurate assessment of these outcomes.

Keywords: Chloroquine, Hydroxychloroquine, COVID-19, Adverse effects, Safety, Systematic review

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A cloroquina (CQ) e a hidroxicloroquina (HCQ) foram originalmente desenvolvidas para o tratamento da malária. Devido às propriedades adicionais antiproliferativas, anti-inflamatórias e imunomoduladoras, essas medicações têm sido utilizadas para tratar outras condições como doenças reumatológicas e dermatológicas. Também tem sido estudado seu potencial terapêutico em oncologia, doenças metabólicas e doenças infecciosas (1, 2).

Em 1820, o quinino foi isolado da casca da árvore cinchona. Foi então que, na década de 1930, a partir dos principais elementos estruturais dessa substância, a CQ foi desenvolvida e se tornou um dos principais antimaláricos sintéticos da época. A HCQ foi introduzida em 1946 como o análogo hidroxilado da CQ, apresentando um menor potencial de toxicidade (3). Atualmente, a HCQ tem uma eficácia estabelecida tanto para lúpus eritematoso sistêmico (LES), quanto para artrite reumatoide (AR), fazendo parte do tratamento de primeira linha dessas doenças (4-7).

CQ e HCQ tem uma biodisponibilidade entre 70 e 80%, quando administradas de forma oral, e uma meia vida longa devido ao alto volume de distribuição sérica. Geralmente são absorvidas no trato gastrointestinal superior (8). Ambas se ligam fortemente à melanina, depositando-se em tecidos como a pele e a retina, o que poderia explicar o potencial de tratamento em afecções cutâneas e a retinopatia, uma possível complicação associada a essas drogas (9). A metabolização hepática da CQ e da HCQ pelas enzimas do citocromo P450 justifica a interação com drogas como digoxina e metoprolol, podendo com isso, aumentar a concentração das mesmas e contribuir para o surgimento de eventos adversos cardíacos (10, 11).

Desde a tragédia relacionada a medicação Talidomida em 1961, a princípio utilizada para tratamento de náusea, os eventos adversos das medicações passaram a atrair a atenção da comunidade científica. O uso dessa medicação por gestantes trouxe consequências devastadoras para os fetos, causando graves mal formações de membros, denominadas focomelia e micromelia. A partir de então, agências reguladoras dos países viram a necessidade de coletar relatórios sobre reações adversas de medicamentos e vários programas de monitorização foram iniciados (12).

Eventos adversos são definidos como qualquer ocorrência médica desfavorável que pode ocorrer durante o uso de uma medicação em seres humanos, sem possuir necessariamente relação causal com esse medicamento (13). Reação

adversa a um medicamento, ocorre quando há uma reação nociva e não-intencional a partir do uso de doses habitualmente utilizadas em seres humanos. Enquanto isso, erro de medicação é definido como qualquer erro ocorrido no processo de uso do medicamento, como dosagem e indicação inapropriadas por profissionais de saúde ou pelos próprios pacientes. Dessa forma, eventos adversos compreendem reações adversas que podem ser evitáveis ou não (14).

A notificação dos eventos adversos é baseada na sua categorização de acordo com expectativa, causalidade e gravidade. Eventos inesperados são aqueles que sua natureza e gravidade não são consistentes com as informações documentadas até então. Causalidade diz respeito a possibilidade de que determinado evento esteja realmente relacionado à exposição a um medicamento. Esta avaliação de causalidade pode ser baseada em fatores como plausibilidade biológica, experiência anterior com o produto, relação temporal entre a exposição e o início do evento, bem como relação com sua suspensão e reexposição(15).

Quanto à gravidade, há a classificação em eventos adversos graves (EAG), os quais resultam em morte, risco de vida, internação ou prolongamento de internação hospitalar, sequela persistente ou significativa, redução substancial da capacidade de realizar funções básicas de vida e anomalia congênita/defeitos de nascimento; ou eventos não graves, que compreendem qualquer evento não incluído nos critérios de EAGs (13).

Outros métodos de classificação da severidade dos eventos adversos foram desenvolvidos para diferentes tipos de intervenções, como por exemplo: *Common Terminology Criteria for Adverse Events* (CTCAE), desenvolvido pelo Instituto Nacional de Câncer dos Estados Unidos e a *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*, emitida pela agência de regulação norte americana *Food and Drug Administration* (FDA) (16, 17).

A avaliação da segurança de um novo medicamento envolve algumas etapas. Primeiramente, na fase pré-clínica ou pesquisa experimental, são realizados testes in vitro ou em animais. Inicia-se então a pesquisa clínica, da qual fazem parte quatro fases. A fase I é a primeira avaliação de segurança em seres humanos, envolvendo poucos indivíduos. Na fase II, o objetivo principal é testar a eficácia e estabelecer a dose eficaz da medicação, mas em paralelo, também é avaliada segurança. A fase III

avalia a eficácia comparativa da medicação, além da sua segurança em um maior número de pacientes. Se comprovada eficácia e segurança na fase III, a medicação já pode ser registrada e comercializada (18, 19).

A fase IV ocorre após a comercialização da medicação para a população, aumentando consideravelmente o tempo de uso e o número de indivíduos expostos àquela droga. Essa fase compreende a atuação da farmacovigilância, a qual é definida como a ciência relativa à detecção, avaliação, compreensão e prevenção de efeitos adversos relacionados a medicamentos (20). Ao testar a segurança de um medicamento, estudos de fase III oferecem condições diferentes daquelas encontradas na prática clínica ou na vida real. Na prática clínica, os pacientes não são criteriosamente selecionados e podem utilizar outros medicamentos concomitantemente. Além disso, o tamanho amostral da maioria dos estudos de fase III só permite a detecção dos eventos adversos mais comuns. Por isso, a farmacovigilância se torna uma estratégia fundamental para uma avaliação integral dos eventos adversos relacionados a uma medicação (19, 21).

Em relação à CQ e HCQ, pelo seu longo tempo de uso na população, há um perfil de segurança mais estabelecido tanto para malária, quanto para doenças reumatológicas. Os eventos adversos mais comuns dessas medicações estão relacionados à intolerância gastrointestinal, incluindo vômitos, náusea, diarreia, dor abdominal, redução do apetite e perda de peso (22, 23).

Manifestações cutâneas, tais como prurido, *rash* cutâneo, fotossensibilidade e hiperpigmentação, além de queda de cabelos foram efeitos colaterais relatados da CQ e da HCQ. Outras manifestações cutâneas adversas menos frequentes, como eritrodermia, dermatite esfoliativa, erupções eczematosas e eritema anular centrífugo também já foram reportadas na literatura (23, 24).

Quanto à cardiotoxicidade, CQ e HCQ podem levar a distúrbios de condução cardíaca (bloqueio de ramo, bloqueio atrioventricular), insuficiência cardíaca, hipertrofia ventricular, hipocinesia, disfunção valvar, hipertensão pulmonar e prolongamento do intervalo QT (25). A toxicidade cardíaca pode estar associada à disfunção de enzimas lisossomais, levando ao comprometimento de degradação intracelular e consequente acúmulo de produtos metabólicos (25-27). Outras manifestações menos frequentes que têm sido associadas ao uso da CQ e HCQ são

ototoxicidade (perda auditiva neurossensorial, zumbido e manifestações cocleovestibulares) e miopatia (28, 29).

Um importante eventos adverso associado a esses medicamentos é a retinopatia, um dos efeitos colaterais oculares mais graves e que pode gerar danos visuais irreversíveis. Ela é caracterizada por ser bilateral, podendo apresentar escotoma paracentral no campo visual e defeito na percepção das cores (30). O risco de desenvolvimento dessa alteração é de 1% após o uso crônico de HCQ por 5 anos, aumentando para 2% e 20% quando utilizada por mais de 10 e 20 anos, respectivamente. Dessa forma, recomenda-se rastreamento anual de todos os pacientes após 5 anos de uso de HCQ. Para isso, pode-se utilizar o exame automatizado de campo visual e a tomografia de coerência óptica de domínio espectral para detectar sinais de toxicidade reversível precocemente. Essa toxicidade parece ser dose dependente, e por isso tem-se recomendado como dose diária segura não mais que 5,0 mg/kg de HCQ (31).

Desde a década de 1960, foi identificada a atividade antiviral *in vitro* da CQ e da HCQ. Portanto, a eficácia dessas drogas tem sido estudada em relação a uma variedade de doenças infecciosas agudas, incluindo Zika, influenza A H5N1, Ebola, dengue e chikungunya; além de infecções virais crônicas, como hepatite C e infecção pelo vírus da imunodeficiência humana (HIV) (32-35). Em fevereiro de 2020, foi publicado estudo em que a CQ poderia inibir o vírus SARS-CoV-2 *in vitro* (35).

Diante da crise de saúde instalada com a pandemia da COVID-19 e da ausência de terapia medicamentosa específica até então, CQ e HCQ passaram a ser avaliadas quanto à sua eficácia no tratamento dessa enfermidade. Portanto, com a possibilidade do uso em larga escala dessas medicações, surgiram preocupações quanto aos seus eventos adversos, principalmente aqueles potencialmente fatais (36, 37).

Dessa forma, como esses medicamentos são utilizados há muitas décadas para malária e outras condições, realizamos uma revisão sistemática de ensaios clínicos randomizados para avaliar a segurança de CQ e HCQ na COVID-19 e em diferentes condições.

1. Avaliar a segurança da cloroquina (CQ) e da hidroxicloroquina (HCQ) a partir dos dados publicados de ensaios clínicos randomizados (ECR) de indivíduos com COVID-19 ou outra condição clínica para qual essas medicações foram prescritas.
2. Para os ECR publicados, relacionados a COVID-19, cuja intervenção tenha sido CQ ou HCQ, avaliar a qualidade do relato dos eventos adversos reportados, tendo como base os 10 itens da extensão do *Consolidated Standards of Reporting Trials* (CONSORT) de como reportar os eventos adversos.
3. Avaliar a segurança da CQ e da HCQ, comparando os resultados publicados com os não publicados no que se refere aos números dos desfechos primários.

Esta revisão sistemática da literatura foi realizada de acordo com a *Cochrane Collaboration* (38) e a mesma foi reportada de acordo com o *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) (39). Seu protocolo foi registrado na plataforma de registros de revisões sistemáticas *International Prospective Register of Systematic Reviews* (PROSPERO), base de registro de protocolos de revisões sistemáticas mantida pelo *Centre of Reviews and Dissemination* da Universidade de York e financiada pelo *National Institute for Health Research*, presente nos Documentos Anexos. O código de registro desse projeto na PROSPERO é CRD42020177818.

A revisão envolveu três etapas metodológicas: avaliação da segurança da cloroquina (CQ) e da hidroxiclороquina (HCQ) a partir de dados publicados, avaliação da qualidade do relato dos eventos adversos (EA) reportados e comparação dos resultados publicados com os não publicados.

Avaliação da segurança de CQ e HCQ a partir de dados publicados

CrITÉRIOS de Elegibilidade

Foram selecionados para essa revisão ensaios clínicos randomizados (ECR), cujos critérios de elegibilidade seguiram a estrutura PICO (P: Participantes, I: Intervenção, C: Comparação, O: Desfechos) descrita abaixo:

- **Participantes (P)**

Indivíduos com diagnóstico de COVID-19 ou outra condição, a despeito de gênero ou idade, cujo tratamento tenha sido com CQ ou HCQ.

- **Intervenção (I)**

O uso de CQ ou HCQ foi considerado como intervenção.

- **Comparação (C)**

O grupo comparação foi composto por aqueles indivíduos que não fizeram uso de CQ ou HCQ (placebo ou não intervenção). Os grupos intervenção e comparação deveriam receber o mesmo tratamento padrão para a condição de saúde avaliada. Dessa forma, não foram elegíveis estudos que comparavam grupos usando exclusivamente CQ/HCQ com grupos utilizando exclusivamente outra medicação.

- **Desfechos (O)**

O desfecho primário foi o número de pacientes com eventos adversos graves (EAG), o número de pacientes com retinopatia, e o número de pacientes com complicações cardíacas. Foi considerado como EAG qualquer EA ou reação adversa suspeita que tenha desencadeado: morte, risco de vida, internação hospitalar ou prolongamento de uma internação vigente, sequela persistente ou significativa, redução substancial da capacidade de realizar funções básicas de vida ou uma anomalia congênita/defeitos de nascimento (13).

Foi considerada retinopatia atribuída à CQ ou HCQ, o diagnóstico dessa alteração após o uso dessas medicações em pacientes com exame oftalmológico prévio normal. Foram consideradas complicações cardíacas, com provável associação a CQ ou HCQ: distúrbios de condução e outros eventos adversos cardíacos não específicos (hipertrofia ventricular, hipocinesia, insuficiência cardíaca, hipertensão arterial pulmonar e disfunção valvar) (40).

Os desfechos secundários foram: número de participantes com qualquer efeito adverso relatado e relacionado ao uso de CQ ou HCQ, número de participantes excluídos nos estudos devido eventos adversos relacionados a CQ ou HCQ, número de pacientes com efeitos adversos gastrointestinais (náusea, vômito, dor abdominal, diarreia, redução do apetite e perda de peso), número de pacientes com manifestações cutâneas (*rash* cutâneo, prurido, queda de cabelo, eritrodermia, dermatite esfoliativa, urticária, erupções eczematosas, fotossensibilidade e eritema anular centrífugo), número de pacientes com miopatia, número de pacientes com sintomas visuais e número de pacientes com sintomas auditivos.

Desenho de Estudo

Foram incluídos apenas ECRs.

Tempo de avaliação dos desfechos

Os desfechos foram avaliados em quatro semanas ou após quatro semanas. ECRs com desfechos avaliados em menos de quatro semanas foram combinados com aqueles mais próximos desse prazo (em quatro semanas).

Crítérios de Exclusão

Foram excluídos ensaios clínicos não randomizados, ou estudos cujos grupos de intervenção e de comparação receberam tratamento padrão diferente para doença de base do paciente.

Identificação dos Estudos

Bases de dados eletrônicas

Estratégias gerais de pesquisa foram criadas para os principais bancos de dados eletrônicos de saúde: *Embase* (por *Elsevier*, 1980 a 11 de abril de 2020), *Medline* (por *PubMed*, 1966 a 11 de abril de 2020), *LILACS* (por *Virtual Health Library*, 1982 a 11 de abril de 2020), *Controlled Clinical Trials of Cochrane Collaboration* (*CENTRAL*, 1982 a 11 de abril de 2020), *Trip database*, *SCOPUS*, and *Web of Science* (20 de abril de 2020). Uma segunda busca, em todas as mesmas bases de dados, foi realizada em 11 de abril de 2021.

As estratégias de busca apresentaram termos índices e sinônimos de cloroquina e hidroxicloroquina. No *PubMed*, foram utilizados os filtros para estudos randomizados, conforme a Colaboração Cochrane, e o filtro incorporado foi utilizado para mesma finalidade na *Embase*. Não houve restrições de data (ano) ou idioma. As estratégias de pesquisa mencionadas estão descritas nos Materiais Suplementares.

Para identificação de possíveis estudos elegíveis adicionais, referências de estudos primários e secundários relevantes foram incluídas na pesquisa. Como muitos estudos atenderam aos critérios de elegibilidade, a busca por artigos não publicados ocorreu em um segundo momento.

O software de gerenciamento de citações *Endnote* foi utilizado para baixar referências e remover entradas duplicadas. A triagem inicial de resumos e títulos foi realizada pelo website *Rayyan QCRI* (41).

Coleta de Dados e Análise

Seleção dos Estudos

Dois revisores (MSB e VSNN), independentemente, selecionaram estudos potencialmente elegíveis para inclusão na revisão de acordo com títulos e resumos. Os estudos selecionados nessa fase foram lidos na íntegra e avaliados quanto a sua

adequação à estrutura 'PICO' proposta. Em casos de desacordo, foram realizadas reuniões de consenso entre os revisores para uma decisão final.

Extração e gerenciamento de dados

Os dois revisores (MSB e VSNN), independentemente, utilizaram um formulário padrão para extrair os seguintes dados dos estudos selecionados: ano de publicação, país, ECR pragmáticos ou não pragmáticos, doença de base dos participantes, grupos de população (crianças, adultos, gestantes), tamanho da amostra, tempo de seguimento, tipo de intervenção e comparação, dose diária da medicação da intervenção, número de pacientes randomizados para o grupo intervenção e comparação, número de eventos no grupo intervenção e comparação para cada desfecho primário e secundário estudado e idade média dos participantes.

Para os desfechos específicos, o número de eventos foi considerado zero apenas se os autores mencionaram que esses eventos não foram evidenciados em qualquer paciente daquele grupo. Caso contrário, foi interpretado que os autores não avaliaram esses desfechos.

Para garantir consistência entre os revisores, realizamos um exercício de calibração antes de iniciar a revisão. Nos casos de publicações duplicadas ou de vários artigos do mesmo estudo primário, a extração de dados foi otimizada, utilizando as melhores informações disponíveis para todos os itens do estudo. Em casos de desacordo, houve uma discussão entre os revisores antes da classificação final.

Avaliação do risco de viés nos estudos incluídos

Para cada estudo selecionado, o risco de viés dos desfechos primários foi avaliado de acordo com os critérios descritos na ferramenta revisada de risco de viés da Cochrane para ensaios clínicos randomizados (RoB 2 *tool*) (42), a qual considera, para cada desfecho avaliado, cinco domínios: (1) viés decorrente do processo de randomização, (2) viés devido a desvios das intervenções propostas, (3) viés por falta de dados do desfecho, (4) viés na aferição do desfecho e (5) viés na seleção dos desfechos relatados. Cada um dos itens foi avaliado em pares, independentemente, e classificado como baixo, alto risco ou alguma preocupação em relação à presença do risco de viés em agosto de 2020 e junho de 2021.

Em relação ao domínio 3, consideramos que o desfecho primário EAG teria um resultado disponível para todos ou quase todos os participantes, quando houvesse menos de 5% de perda de seguimento no estudo, resultando em um baixo risco de viés. Para os estudos em que a perda de seguimento ocorreu em mais de 5% dos participantes, também consideramos um baixo risco de viés neste domínio se as taxas de perda foram equilibradas entre os grupos (intervenção e comparação), se as causas foram justificadas e não relacionadas com qualquer EAG.

Para desfechos em que os avaliadores estavam cientes da intervenção recebida pelos participantes do estudo, consideramos que as avaliações de retinopatia e de complicações cardíacas podem ter sido influenciadas pelo conhecimento da intervenção, mas não para EAG. Para complicações cardíacas, em estudos abertos, em que não havia a informação de que todos os participantes foram submetidos ao mesmo método e frequência de investigação, consideramos que a aferição ou determinação dos resultados poderia ser diferente entre os grupos de intervenção e controle.

Unidade de análise

Para o primeiro objetivo, os dados publicados nos estudos incluídos foram a unidade de análise. Utilizamos os dados disponíveis em artigos publicados, preferencialmente, os dados de análise por intenção de tratar. Para os estudos que não forneceram análise por intenção de tratar, consideramos o número de pacientes randomizados em cada grupo e, para pacientes que perderam seguimento nessa situação, determinamos o evento adverso avaliado como ausente (43). Para os ensaios clínicos com múltiplos braços, selecionamos apenas os grupos em que a intervenção (CQ ou HCQ) e o controle (placebo ou sem intervenção) receberam os mesmos tratamentos padrão para a doença de base do paciente. Para os ensaios clínicos com múltiplos braços e diferentes regimes de doses, combinamos os grupos em que CQ ou HCQ foram administrados.

Para os ECR por cluster, utilizamos uma fórmula sugerida pelo manual da Cochrane para encontrar o tamanho amostral efetivo, que é o tamanho amostral original dividido pelo *design effect*. O *design effect* pode ser calculado por $1 + (M - 1) \times ICC$, em que M é a média do tamanho do cluster e ICC é o coeficiente de correlação intracluster (38).

Análise de Dados

Resultados semelhantes foram plotados na meta-análise por meio do *Stata Statistical Software 17* (*Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC*). O risco relativo (RR) foi calculado com um intervalo de confiança (IC) de 95% como estimativa do efeito da intervenção (CQ ou HCQ) e um modelo de efeitos aleatórios foi utilizado para as meta-análises (38).

Como essa revisão sistemática envolveu avaliação de segurança, para evitar subestimar danos, utilizamos o método de Peto para eventos com taxas menores que 1%. O método de Peto utiliza uma abordagem de variância inversa, porém com um método aproximado para estimar o log do *odds ratio* (OR). Essa aproximação funciona bem quando os efeitos da intervenção são pequenos (OR próximo a 1), quando os eventos não são comuns e quando os estudos têm números semelhantes nos grupos de intervenção e controle. Estudos em que nenhum evento foi observado em ambos os braços, tanto da intervenção, quanto do controle, foram excluídos da meta-análise, já que a nossa revisão envolve eventos adversos (44).

Análise de sensibilidade

Para EAG, realizamos uma análise de sensibilidade de acordo com o risco de viés (“alto risco” *versus* “algumas preocupações” *versus* “baixo risco”), de acordo com o grupo de comparação (placebo *versus* sem intervenção) e de acordo com o tamanho amostral (≥ 100 participantes *versus* < 100 participantes). Para EAG e complicações cardíacas, adicionamos análise por protocolo.

Análise de subgrupo

Para EAG, realizamos análises de subgrupo de acordo com tipo de intervenção (CQ ou HCQ), diagnóstico do paciente, tipo de população (crianças, adultos e gestantes), dose diária (< 500 mg *versus* ≥ 500 mg para CQ, < 400 mg *versus* ≥ 400 mg para HCQ) e tempo de seguimento ($\leq$ quatro semanas *versus* $>$ quatro semanas).

Utilizamos o instrumento *Credibility of Effect Modification Analyses* (ICEMAN) para avaliação da credibilidade dos subgrupos. A modificação de efeito, realizada por análise de subgrupo, avalia se o efeito de uma intervenção varia de acordo com alguma variável. Essa análise pode não ser verdadeira, já que a diferença de efeito muitas vezes ocorre simplesmente pelo acaso, por viés de relato seletivo ou falha em

utilizar uma estatística adequada. Por conta disso, foi desenvolvido o instrumento ICEMAN, o qual possui uma versão para ECRs e outra para meta-análises. A versão para meta-análises contém 8 questões centrais, conforme ANEXO B, cada uma com 4 diferentes tipos de respostas (credibilidade definitivamente reduzida, credibilidade provavelmente reduzida, credibilidade definitivamente aumentada e credibilidade provavelmente aumentada). O instrumento é capaz de concluir determinando quatro tipo de classificações (credibilidade muita baixa, baixa credibilidade, credibilidade moderada e alta credibilidade), as quais correspondem, respectivamente às seguintes probabilidades de que a modificação de efeito existe verdadeiramente: menor que 25%, entre 25% e 50%, entre 51% e 75% e acima de 75% (45).

Avaliação da Heterogeneidade

As inconsistências entre os resultados dos estudos incluídos foram verificadas por inspeção visual dos gráficos em floresta (sem sobreposição dos ICs em relação às estimativas de efeito dos estudos individuais), pela estatística Higgins ou I^2 , na qual $I^2 > 50\%$ indica uma probabilidade moderada de heterogeneidade e pelo teste do qui-quadrado (Chi2), no qual $p < 0.10$ indica heterogeneidade.

Qualidade da evidência

A qualidade de evidência do efeito estimado da intervenção foi avaliada de acordo com o sistema *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) (46). GRADE é uma ferramenta estruturada para avaliar a qualidade de evidência em revisões sistemáticas ou em diretrizes relacionadas ao cuidado em saúde (47). ECRs são considerados como evidência de alta qualidade; no entanto, a confiança na evidência pode diminuir se os estudos tiverem grandes limitações que possam interferir nas estimativas do efeito do tratamento (47). Essas limitações incluem o risco de viés, inconsistência de resultados, evidência indireta, imprecisão e viés de relato seletivo (ou viés de publicação dos resultados) (48).

Avaliação da qualidade do relato dos eventos adversos reportados

Na segunda etapa metodológica, os ECRs incluídos sobre COVID-19 foram avaliados com base nos 10 itens da extensão do *Consolidated Standards Reporting Trials* (CONSORT) de como reportar os eventos adversos (49).

MSB e VSN extraíram dados dos artigos selecionados em relação à aderência de cada estudo às recomendações da extensão do CONSORT, especificadas conforme ANEXO A. Explicações e exemplos fornecidos no documento do CONSORT foram utilizados como guias. As discrepâncias foram resolvidas por discussão entre MSB e VSN. Cada estudo foi avaliado como “sim” ou “não”, de acordo com a aderência às recomendações de cada item da extensão do CONSORT, conforme modelo de extração no APÊNDICE A.

Comparação dos resultados publicados com os não publicados

Para a terceira etapa metodológica, foi utilizada a mesma estratégia de busca da primeira etapa para pesquisar resultados não publicados de novembro de 2004, quando surgiu a extensão do CONSORT de como reportar eventos adversos, até 11 de abril de 2021.

A pesquisa foi realizada nas bases de dados *Web of Science* e *Google Schollar*. Foi estabelecido que seriam avaliados os primeiros 100 resultados do *Google Schollar*. Anais de congressos foram pesquisados na *Web of Science Conference Proceedings Citation Index – Science* (CPCI-S). Teses e dissertações foram pesquisadas na Biblioteca Digital Brasileira de Teses e Dissertações (BDTD), Catálogo de Teses e Dissertações da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Biblioteca Digital de Teses e Dissertações da Universidade de São Paulo (USP) e Repositório Institucional da Universidade Estadual Paulista “Júlio de Mesquita Filho” (UNESP). Além disso, foram realizadas buscas nos sites de agências reguladoras: Agência Nacional de Vigilância Sanitária (ANVISA), *Food and Drug Administration* (FDA) e *European Medicines Agency* (EMA).

Foram utilizados os dados publicados e não publicados como unidade de análise e a avaliação, nessa etapa, foi referente aos desfechos primários: número de pacientes com EAG, número de pacientes com retinopatia, e número de pacientes com complicações cardíacas.

RESEARCH

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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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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 a random-effects model to pool results across studies and Peto's 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: One hundred and six 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]: 0.76–1.26, 33 trials, 15,942 participants, moderate certainty of evidence). However, there was a moderate certainty of evidence that CQ/HCQ increases the incidence of cardiac complications (RR: 1.62, 95% CI: 1.10–2.38, 16 trials, 9908 participants). 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).

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Conclusions: CQ and HCQ probably do not increase SAEs, with low frequency of these adverse events on malarial and non-malarial conditions. However, they may increase cardiac complications especially in patients with COVID-19. No clear effect of their use on the incidence of retinopathy was observed.

Systematic review registration: PROSPERO [CRD42020177818](https://www.crd42020177818)

Keywords: Chloroquine, Hydroxychloroquine, COVID-19, Adverse effects, Safety, Systematic review

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 side effects associated with CQ and HCQ [8].

A 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 studies that meet the “PICOS” 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 the 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.

Study design (S)

We included only RCTs.

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 the patient's basal disease.

Identification of studies

Electronic databases

General search strategies were applied to the main electronic health databases: Embase (Elsevier, 1980–11th April 2020), Medline (PubMed, 1966–11th April 2020), LILACS (Virtual Health Library, 1982–11th April 2020), CENTRAL (Controlled Clinical Trials of Cochrane Collaboration, 1982–11th April 2020), Trip database, SCOPUS, and Web of Science (20th April 2020). A second search on all databases was conducted on 11th April 2021. 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](#). References of relevant primary and secondary studies were searched to identify additional eligible studies. As a huge number of studies met our eligibility criteria, the search for unpublished sources (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) independently 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 the measurement of the outcome, (5) bias in the selection of the reported result. For cluster randomized trials we used a specific Rob2 tool for cluster RCTs. 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” on 10th August 2020 and 8th June 2021. We classified SAEs as the 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 open-label 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 might be different between the groups.

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]. For the multi-arm trials, we only selected the groups in which the intervention (HCQ/CQ) and the control (non-intervention or placebo) received the same standard treatments for the patient's basal disease. For the multi-arm trials with different regimen doses, we combined the groups in which CQ/HCQ were administered.

For the cluster randomized trials, we used a formula suggested by the Cochrane handbook to find the trial's effective sample size, which is its original sample size divided by the “design effect.” The design effect can be calculated by $1 + (M - 1) \times ICC$, where M is the average cluster size and ICC is the intracluster correlation coefficient [12].

Data analyses

Similar outcomes were plotted in the meta-analysis using the Stata Statistical Software 17 (Stata Statistical Software: Release 17. 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's 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 analyses according to the risk of bias (“high risk” versus “some concerns” versus “low risk”), according to the comparison group (placebo versus no CQ/HCQ), and sample size (≥ 100 participants versus < 100 participants). For SAE and cardiac complications, we added per-protocol analyses.

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 (< 500 mg versus ≥ 500 mg for CQ, < 400 mg versus ≥ 400 mg for HCQ), time of follow up (≤ 4 weeks versus > 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

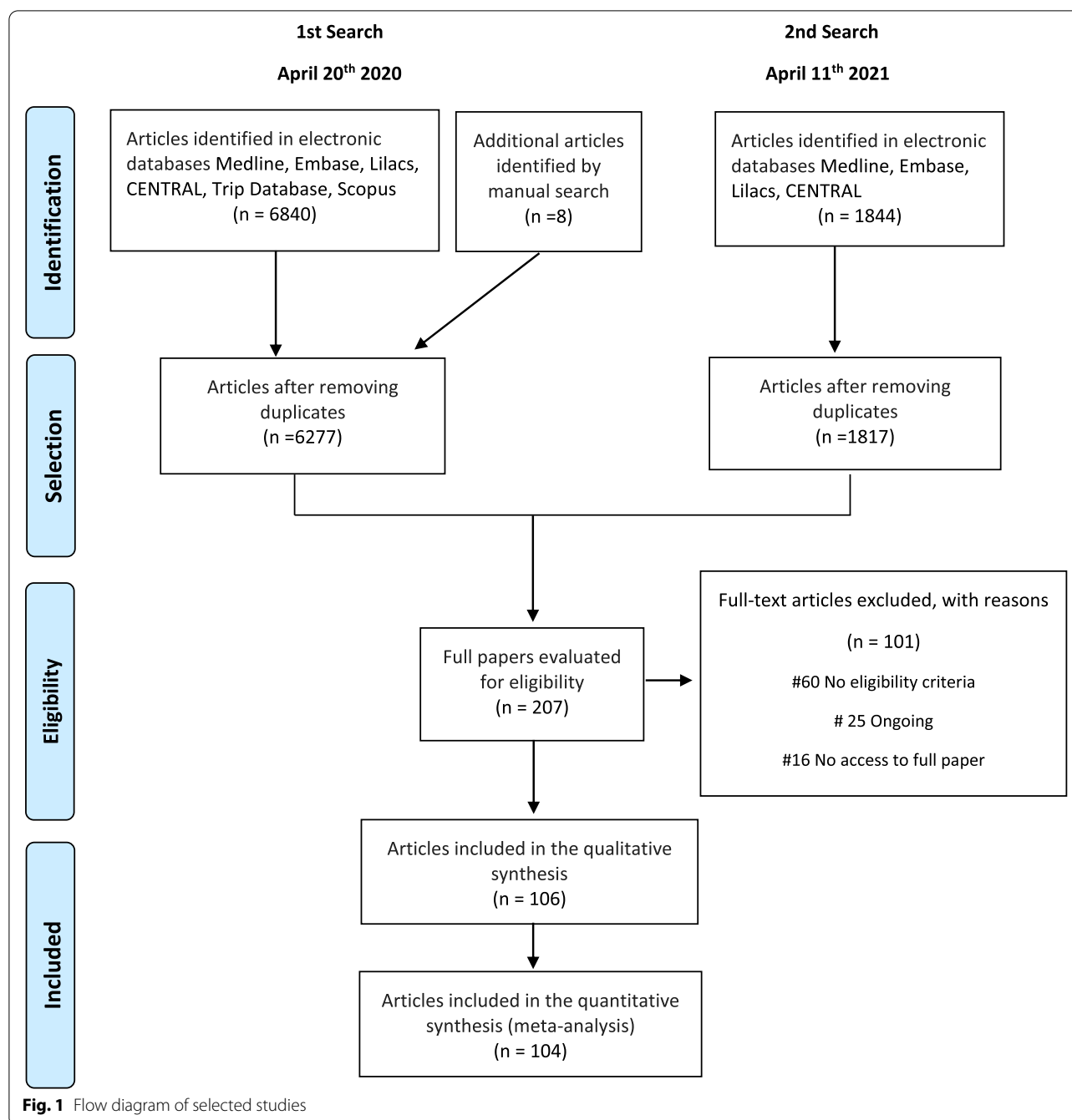
Inconsistencies between the results of the studies included were ascertained by visual inspection of forest plots (no overlap of CIs around the effect estimates of the individual studies) and by Higgins or I^2 statistic, in which $I^2 > 50\%$ indicated a moderate probability of heterogeneity, and by chi-squared tests (χ^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]. GRADE is a structured process for rating the quality of evidence in systematic reviews or in guidelines for health care [21]. Randomized controlled trials begin as high-quality evidence; however, the confidence in the evidence may decrease if the studies have major limitations that may interfere with the estimates of the treatment effect [21]. These limitations include the risk of bias, inconsistency of results, indirectness of evidence, imprecision, and reporting bias [22].

Results

The search strategies yielded different studies, and after removing duplicates, 8094 studies remained. We selected 207 studies that had a high probability of meeting our



inclusion criteria for a complete examination (Fig. 1). After completely examining these references, 106 studies met our eligibility criteria and therefore were included in this review.

A total of 101 studies were excluded for the following reasons: no AE was evaluated ($n = 40$), no control

group as placebo or non-comparator for CQ or HCQ ($n = 9$), non-RCT ($n = 5$), 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 106 studies included, 20 were on COVID-19 [23–42], 13 studies were on malaria [43–55], 11 on other infectious conditions [56–67], 31 were on rheumatology [68–98], four on dermatologic diseases [99–102], eight on cancer [103–110], seven were on metabolic disease [111–117], and the remaining were on other conditions [118–128]. Seventy-one studies used HCQ (17,911 participants) as intervention and 35 used CQ (6997 participants). Most studies used placebo as a comparator, seven studies were on children [43, 44, 46, 49, 52, 70, 106], two on pregnant women [55, 90], and the others were on the adult population. Most studies used daily intervention doses ≥ 500 mg for CQ and ≥ 400 mg for HCQ. Rajasinghan et al.'s trial was the only multi-arm trial whose groups received different doses of the same intervention [39]. We combined the groups in which HCQ were administered. We included one cluster randomized trial, Mitjà et al, in the meta-analyses [37].

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 1 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. XIX and Fig. XX in the [Supplementary file](#), respectively, present the risk of bias for retinopathy and cardiac complications. Regarding SAEs, most studies were assessed as low risk of bias, while some were classified as some concerns or high risk due mainly to randomization process or missing outcome data. For retinopathy, most studies did not mention the method used to evaluate this outcome, and because of that, they were classified mostly as some concerns or high risk of bias. For cardiac complications, the open-label RCTs were graduated as some concerns of risk of bias due to no information if participants of both groups were submitted to the same method and frequency of the outcome evaluation.

Meta-analysis

Regarding primary outcomes, there is no evidence to support the difference between CQ/HCQ and the control group (placebo or non-CQ/HCQ) with regard to the frequency of SAE (OR: 0.98, 95% CI: 0.76–1.26, 33 studies, 15,942 participants, moderate certainty of evidence, Table 2, Fig. 3). Forty BAOE studies with 5440 participants were excluded from this analysis (Fig. 3). Applying

the GRADE approach, due to non-inclusion of unpublished data, the quality of evidence was rated down in one level.

Regarding the association between CQ/HCQ and the frequency of retinopathy, the evaluation of the risk of bias 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 2). Twenty BAOE studies with 1559 participants were excluded from this analysis (Fig. 4).

The meta-analysis showed that HCQ increases the incidence of cardiac complications (RR: 1.62, 95% CI: 1.1–2.38, 16 trials, 9908 participants, moderate certainty of evidence, Fig. 5, Table 2), six BAOE studies were excluded from this analysis. Out of the 16 RCTs included in this meta-analysis, 11 were in COVID-19 patients (10,390 participants). Applying Rob2, the open-label RCTs were evaluated considering some concerns about the risk of bias in the measurement of this outcome. It occurred because there is no information if participants of both groups were submitted to the same method and frequency of the evaluation of cardiac complications. Consequently, the quality of evidence was rated down. 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, 85]. The sensitivity analysis per protocol did not change the effect size of HCQ in these outcomes ([Supplementary file](#)).

For the secondary outcomes, the administration of CQ/HCQ increases the incidence of total AE (RR 1.45, 95% CI: 1.26–1.69, 51 studies, 13,034 participants, [Supplementary file](#)), nausea/vomiting (RR 1.93 95% CI: 1.51–2.49, 26 studies, 7981 participants, [Supplementary file](#)), diarrhea (RR 2.04% CI: 1.41–2.93, 23 studies, 8378 participants, [Supplementary file](#)), withdrawal due to AE (RR 1.38, 95% CI: 1.12–1.71, 41 studies, 7472 participants, [Supplementary file](#)), auditory symptoms (RR 1.82, 95% CI: 1.09 to 3.03, 9 studies, 5199 participants) and dermatological affections (RR 1.62, 95% CI: 1.18–2.23, 20 studies, 7026 participants, [Supplementary file](#)). There was no clear evidence to support a difference between the CQ/HCQ and control group with regard to visual symptoms and headache (RR 1.59, 95% CI: 1.00 to 2.54, 26 studies, 9210 participants; RR 1.47, 95% CI: 1.02–2.13, 29 studies, 9953 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

Table 1 Data extracted from included studies

Author	Year	Country	Multicenter	Study design	Population	Condition	Intervention	Comparator	Dosage ≥ 400 mg/day	Treatment time > 4weeks	Randomized patients
Type of intervention: Hydroxychloroquine (HCQ)											
Achuthan	2014	India	No	RCT crossover	Adult	Other	HCQ	No CQ/HCQ	Yes	No	8
Abella	2021	USA	Yes	RCT	Adult	COVID-19	HCQ	Placebo	Yes	Yes	132
Barnabas	2021	USA	Yes	RCT	Adult	COVID-19	HCQ	Placebo	Yes	No	829
Blackburn	1995	USA	Yes	RCT	Adult	Rheumatology	HCQ	Placebo	Yes	Yes	242
Bonfante	2008	Brazil	No	RCT	Adult	Rheumatology	HCQ	Placebo	Yes	Yes	32
Boon-piyathad	2017	Thailand	No	RCT	Adult	Dermatology	HCQ	Placebo	Yes	Yes	55
Boulware	2020	USA, Canada	Yes	Pragmatic	Adult	COVID-19	HCQ	Placebo	Yes	No	821
Brazil	2020	UK	Yes	RCT	Elderly	Oncology	HCQ	Placebo	Yes	Yes	54
Brewer	1986	USA, UKSS	Yes	RCT	Children	Rheumatology	HCQ	Placebo	Variable	Yes	108
Bunch	1984	USA	No	RCT	Adult	Rheumatology	HCQ	Placebo	Variable	Yes	38
Cavalcanti	2020	Brazil	Yes	RCT	Adult	COVID-19	HCQ	No CQ/HCQ	Yes	No	448
Chakravarti	2021	India	No	RCT	Adult	Metabolic disease	HCQ	placebo	Yes	Yes	326
Charous	1998	USA	No	RCT	Adult	Others	HCQ	Placebo	Variable	Yes	17
Chen Jun	2020	China	No	RCT	Adult	COVID-19	HCQ	No CQ/HCQ	Yes	No	30
Chen Zhao-wei	2020	China	No	RCT	Adult	COVID-19	HCQ	Placebo	Yes	No	62
Cheng-Pin Chen	2020	China	Yes	RCT	Adult	COVID-19	HCQ	No CQ/HCQ	Yes	No	33
Clark	1993	Mexico	No	RCT	Adult	Rheumatology	HCQ	Placebo	Yes	Yes	126
Das	2007	India	Yes	RCT	Adult	Rheumatology	HCQ	Placebo	Yes	Yes	122
Davis	1991	UK	No	RCT	Adult	Rheumatology	HCQ	Placebo	Yes	Yes	104
Desta	2002	Ethiopia	No	RCT	Adult	Others	HCQ	Placebo	No	Yes	61
Dubée	2021	France	Yes	RCT	Adult	COVID-19	HCQ	Placebo	Yes	No	250
Erkan	2018	USA, Greece, China	Yes	RCT	Adult	Rheumatology	HCQ	No CQ/HCQ	Yes	Yes	20
Esdaile	1995	Canada	Yes	RCT	Adult	Rheumatology	HCQ	Placebo	Yes	Yes	119
Faarvang	1993	Denmark	Yes	RCT	Adult	Rheumatology	HCQ	Placebo	No	Yes	60
Fong	2007	USA	No	RCT	Adult	Others	HCQ	Placebo	Yes	Yes	102
Gerstein	2002	Canada	No	RCT	Adult	Metabolic disease	HCQ	Placebo	Yes	Yes	135
Gilman	2012	USA	Yes	RCT	Children	Oncology	HCQ	Placebo	Variable	Yes	54
Gottenberg	2014	France	Yes	Pragmatic	Adult	Rheumatology	HCQ	Placebo	Yes	Yes	120
Haar	1993	Denmark	No	RCT	Adult	Rheumatology	HCQ	Placebo	No	Yes	52
Horne	2020	UK/France	Yes	RCT	Adult	Oncology	HCQ	No CQ/HCQ	Yes	Yes	62

Table 1 (continued)

Johnston	2021	USA	Yes	RCT	Adult	COVID-19	HCQ	Placebo	Yes	No	154
Jokar	2013	Iran	No	RCT	Adult	Rheumatology	HCQ	Placebo	Yes	Yes	51
Karasic	2019	USA	Yes	RCT	Adult	Oncology	HCQ	No CQ/HCQ	Yes	No	112
Kavanaugh	1997	USA	No	RCT	Adult	Rheumatology	HCQ	Placebo	Yes	Yes	11
Kingsbury	2018	England	Yes	Pragmatic	Adult	Rheumatology	HCQ	Placebo	Yes	Yes	248
Kraak	1965	The Netherlands	No	RCT	Adult	Rheumatology	HCQ	Placebo	Yes	Yes	49
Kravvariti	2020	Greece	No	RCT	Adult	Rheumatology	HCQ	No CQ/HCQ	Yes	Yes	50
Kruize	1993	Netherlands	Yes	RCT cross over	Adult	Rheumatology	HCQ	Placebo	Yes	Yes	19
Lee	2018	Netherlands	Yes	RCT	Adult	Rheumatology	HCQ	Placebo	Yes	Yes	202
Levy	2001	Brazil	No	RCT	Pregnant	Rheumatology	HCQ	Placebo	No information	Yes	20
Liu	2019	China	No	RCT	Adult	Others	HCQ	Placebo	Yes	Yes	60
Lyngbakken	2020	Norway	Yes	Pragmatic	Adult	COVID-19	HCQ	No CQ/HCQ	Yes	No	53
Majzoobi	2018	Iran	No	RCT	Adult	Infectious conditions	HCQ	No CQ/HCQ	Variable	Yes	177
Mitjå	2020	Spain	Yes	RCT	Adult	COVID-19	HCQ	No CQ/HCQ	Yes	No	353
Mitjå	2021	Spain	Yes	Cluster	Adult	COVID-19	HCQ	No CQ/HCQ	Yes	No	674 (effective sample size)
Murphy	1987	UK	No	RCT	Adult	Dermatology	HCQ	Placebo	Yes	Yes	31
O'Dell	2002	USA	Yes	RCT	Adult	Rheumatology	HCQ	Placebo	Yes	Yes	113
Omrani	2020	Qatar	Yes	RCT	Adult	COVID-19	HCQ	Placebo	Yes	No	304
Pareek	2015	India	Yes	RCT	Adult	Metabolic disease	HCQ	Placebo	No	Yes	328
Paton	2012	UK	No	RCT	Adult	Infectious conditions	HCQ	Placebo	Yes	Yes	83
Quatraro	1990	Italy	No	RCT	Adult	Metabolic disease	HCQ	Placebo	Yes	Yes	38
Rajasingham	2020	USA, Canada	Yes	RCT	Adult	COVID-19	HCQ	Placebo	Yes	Yes	1483
Recovery	2020	UK	Yes	Pragmatic	Adult	COVID-19	HCQ	No CQ/HCQ	Yes	No	4716
Reeves	2004	Australia	No	RCT	Adult	Dermatology	HCQ	Placebo	No information	Yes	21
Reis	2021	Brazil	Yes	RCT	Adult	COVID-19	HCQ	Placebo	Yes	No	441
Roberts	1988	UK	No	RCT cross over	Adult	Others	HCQ	Placebo	Yes	Yes	9
Sarzi-Puttini	2003	Italy	Sim	RCT	Adult	Rheumatology	HCQ	No CQ/HCQ	Yes	Yes	71
Scott	1989	England	Yes	RCT	Adult	Rheumatology	HCQ	Placebo	Yes	Yes	101
Self	2020	USA	Yes	RCT	Adult	COVID-19	HCQ	Placebo	Yes	No	479
Skipper	2020	USA, Canada	Yes	RCT	Adult	COVID-19	HCQ	Placebo	Yes	No	491
Snook	1981	USA	No	RCT	Adult	Others	HCQ	No CQ/HCQ	Yes	No	50

Table 1 (continued)

Sperber	1995	USA	No	RCT	Adult	Infectious conditions	HCQ	Placebo	Yes	40	
Tang	2020	China	Yes	RCT	Adult	COVID-19	HCQ	No CQ/HCQ	Yes	150	
Toledo	2021	USA	No	RCT	Adult	Metabolic disease	HCQ	Placebo	Yes	34	
Ulrich	2020	USA	Yes	RCT	Adult	COVID-19	HCQ	Placebo	Yes	128	
Van Gool	2001	Netherlands	Yes	RCT	Adult	Others	HCQ	Placebo	Yes	168	
Van Jaarsveld	2000	Netherlands	Yes	RCT	Adult	Rheumatology	HCQ	No CQ/HCQ	Yes	187	
Wasko	2015	USA	No	RCT	Adult	Metabolic disease	HCQ	Placebo	Yes	33	
Yokogawa	2017	Japan	Yes	RCT	Adult	Rheumatology	HCQ	Placebo	Yes	103	
Yoon	2016	Korea	No	RCT	Adult	Rheumatology	HCQ	Placebo	Yes	39	
Zeh	2020	USA	No	RCT	Adult	Oncology	HCQ	No CQ/HCQ	Yes	98	
Author	year	Country	Multicenter	Study design	Population	Condition	Intervention	Comparator	Dosage ≥ 500 mg/day	Treatment time > 4 weeks	Randomized patients
Type of intervention: Chloroquine (CQ)											
Arnaout	2019	Canada	No	RCT	Adult	Oncology	CQ	Placebo	Yes	Variable (2–6 weeks)	70
Briceno	2003	Mexico	No	RCT	Adult	Oncology	CQ	No CQ/HCQ	No	Yes	18
Cox	2013	Gambia	No	Cluster	Children	Malaria	CQ	Placebo	Variable	Yes	96
Dunyo	2006	Gambia	No	RCT	Children	Malaria	CQ	No CQ/HCQ	Variable	No	374
Endy	2019	USA	No	RCT	Adult	Malaria	CQ	No CQ/HCQ	Yes	Yes	50
Engchanil	2006	Thailand	No	RCT	Children	Infectious conditions	CQ	No CQ/HCQ	Variable	Yes	46
Fernando	2006	Sri Lanka	No	RCT	Children	Malaria	CQ	Placebo	No	Yes	587
Ferraz	1994	Brazil	Yes	RCT	Adult	Rheumatology	CQ	Placebo	No	Yes	82
Freedman	1960	UK	No	RCT	Adult	Rheumatology	CQ	Placebo	No	Yes	107
Fryauff	1995	Indonesia	No	RCT	Adult	Malaria	CQ	Placebo	No	Yes	78
Galatas	2017	Mozambique	No	RCT	Adult	Malaria	CQ	Placebo	Variable	No	112
Gasasira	2003	Uganda	No	RCT	child/adult	Malaria	CQ	Placebo	Variable	No	341
Gibson	1987	UK	No	RCT	Adult	Rheumatology	CQ	No CQ/HCQ	No	Yes	52
Jacobs	1963	USA	No	RCT	Adult	Dermatology	CQ	Placebo	No	Yes	50
Jacobson	2016	USA	No	RCT cross over	Adult	Infectious conditions	CQ	Placebo	No	Yes	70
Kamgno	2010	Cameroon	No	RCT	Adult	Infectious conditions	CQ	Placebo	Yes	Yes	40
Lamballerie	2008	France	No	RCT	Adult	Infectious conditions	CQ	Placebo	Yes	Yes	54

Table 1 (continued)

McGill	2019	USA	No	RCT	Adult	Metabolic disease	CQ	Placebo	No	Yes	116
Meinão	1996	Brazil	No	RCT	Adult	Rheumatology	CQ	Placebo	No	Yes	24
Michel	2010	France	No	RCT	Adult	Malaria	CQ	Placebo	No	Yes	1010
Miller	2013	USA	No	RCT	Adult	Malaria	CQ	Placebo	Yes	No	38
Miranda	2004	Mexico	Yes	RCT	Adult	Rheumatology	CQ	Placebo	No	Yes	149
Ndyomugy-enyi	2004	Uganda	No	RCT	Children/Adults	Malaria	CQ	No CQ/HCC	Variable	No	88
Pappaioanou	1986	USA	No	RCT	Adult	Infectious conditions	CQ	No CQ/HCC	No	Yes	51
Parrow	1967	Sweden	No	RCT	Adult	Other	CQ	Placebo	No	Yes	18
Paton	2011	Singapore	No	RCT	Adult	Infectious conditions	CQ	Placebo	No	Yes	1516
Peymani	2016	Iran	No	RCT	Adult	Infectious conditions	CQ	Placebo	No	Yes	12
Rojas-puentes	2013	Mexico	No	RCT	Adult	Oncology	CQ	Placebo	No	No	76
Salako	1992	Nigeria	No	RCT	Adult	Malaria	CQ	Placebo	No	Yes	229
Soltani	2007	Iran	No	RCT	Adult	Others	CQ	Placebo	No	Yes	24
Sotelo	2006	Mexico	No	RCT	Adult	Oncology	CQ	Placebo	No	Yes	30
Terrabuio	2018	Brazil	No	RCT	Adult	Others	CQ	Placebo	No	Yes	62
Tricou	2010	Vietnam	No	RCT	Adult	Infectious conditions	CQ	Placebo	Yes	No	307
Vicente	2019	USA	No	RCT	Adult	Malaria	CQ	Placebo	Yes	No	20
Villegas	2007	Thailand	No	RCT	Pregnant	Malaria	CQ	Placebo	No	Yes	1000

Legend: HCC hydroxychloroquine, CQ chloroquine, RCT randomized controlled trial

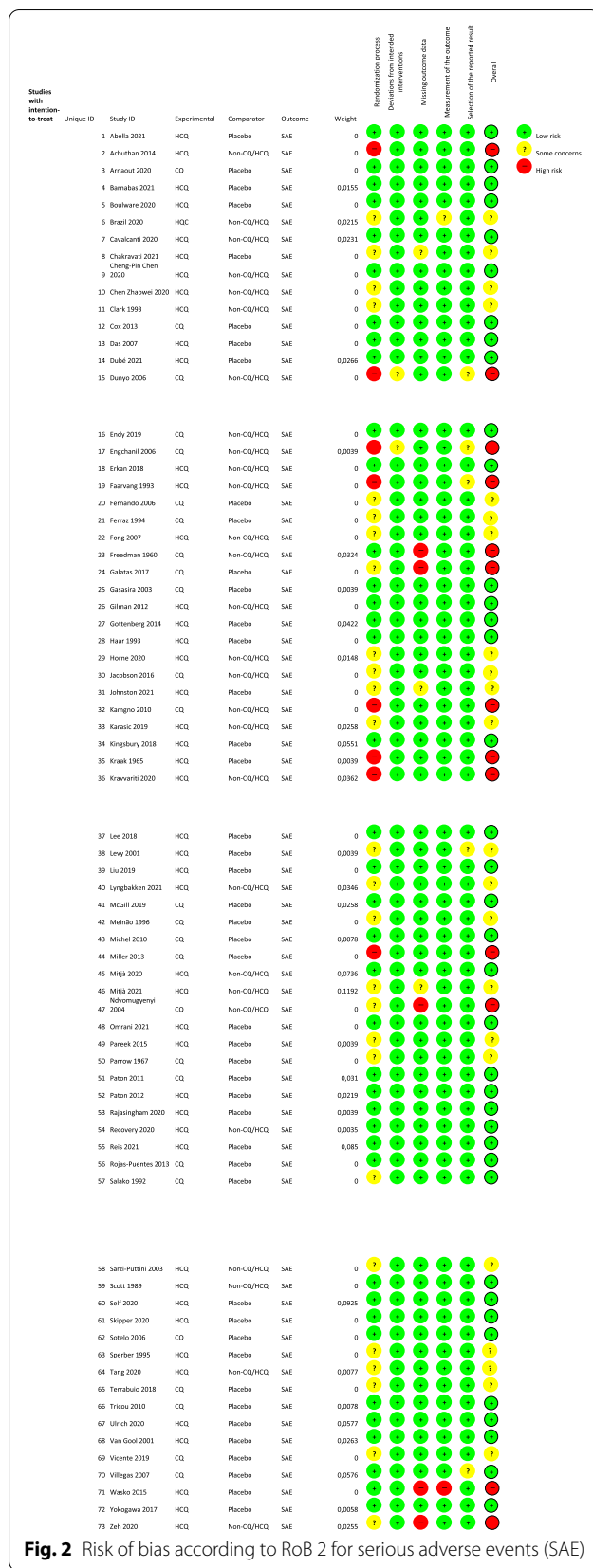


Fig. 2 Risk of bias according to RoB 2 for serious adverse events (SAE)

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 the 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 106 RCTs, with a total of 24,879 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. However, the HCQ increased the incidence of cardiac complications in the trials whose condition was COVID-19. Due to imprecision and risk of bias, we did not observe any clear effect of CQ/HCQ on retinopathy.

Although the literature has reported several CQ/HCQ-associated AEs, both drugs are generally considered safe [129–132]. One of the explanations that HCQ increased the incidence of cardiac complication is that COVID-19 patients have been considered at an increased risk of cardiac arrhythmias [133]. Moreover, some tachyarrhythmias have been observed in this population, being atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation the most frequent [133]. A systematic review under conditions other than COVID-19 identified 86 case/series studies, providing information on 127 participants with cardiac complications likely to be 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

Table 2 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 ^a (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo/non-comparator	Risk with HCQ/CQ				
SAE	14 per 1.000	15 per 1.000 (12 to 20)	OR 0.98 (0.76 to 1.26)	15942 (33 RCTs)	⊕⊕⊕○ MODERATE ^a	CQ/HCQ likely does not increase SAE.
Retinopathy	18 per 1.000	28 per 1.000 (7 to 105)	OR 1.63 (0.40 to 6.57)	344 (5 RCTs)	⊕⊕○○ LOW ^b	The evidence is very uncertain about the effect of CQ/HCQ on retinopathy.
Cardiac Complications	20 per 1.000	37 per 1.000 (25 to 55)	RR 1.62 (1.10 to 2.38)	9908 (16 RCTs)	⊕⊕⊕○ MODERATE ^c	CQ/HCQ may result in an increase in cardiac complications.

^aThe 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, *OR* odds ratio, *RR* risk ratio, *SAE* serious adverse events, *CQ* chloroquine; *HCQ* hydroxychloroquine, *GRADE* Grading of Recommendations Assessment, Development, and Evaluation

GRADE levels 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 The quality of evidence was rated down due to non-inclusion of unpublished data

^b 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 detection of this outcome is 4533 (level of significance = 5%; power = 1 - β = 80%). Then, the optimal information size criterion was not met, and the confidence interval was wide. Because of this the quality of evidence was rating down for imprecision

^c The open-label RCTs were graduated as some concerns of risk of bias due to no information if participants of both groups were submitted to the same method and frequency of the outcome evaluation

(median, 1235 g and 803 g for hydroxychloroquine and chloroquine, respectively). Conduction disorders were the main cardiac complication reported, affecting 85% of the patients. Moreover, the authors highlighted that case/series studies 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 2137 participants and 1096 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 [134]. 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 [135].

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

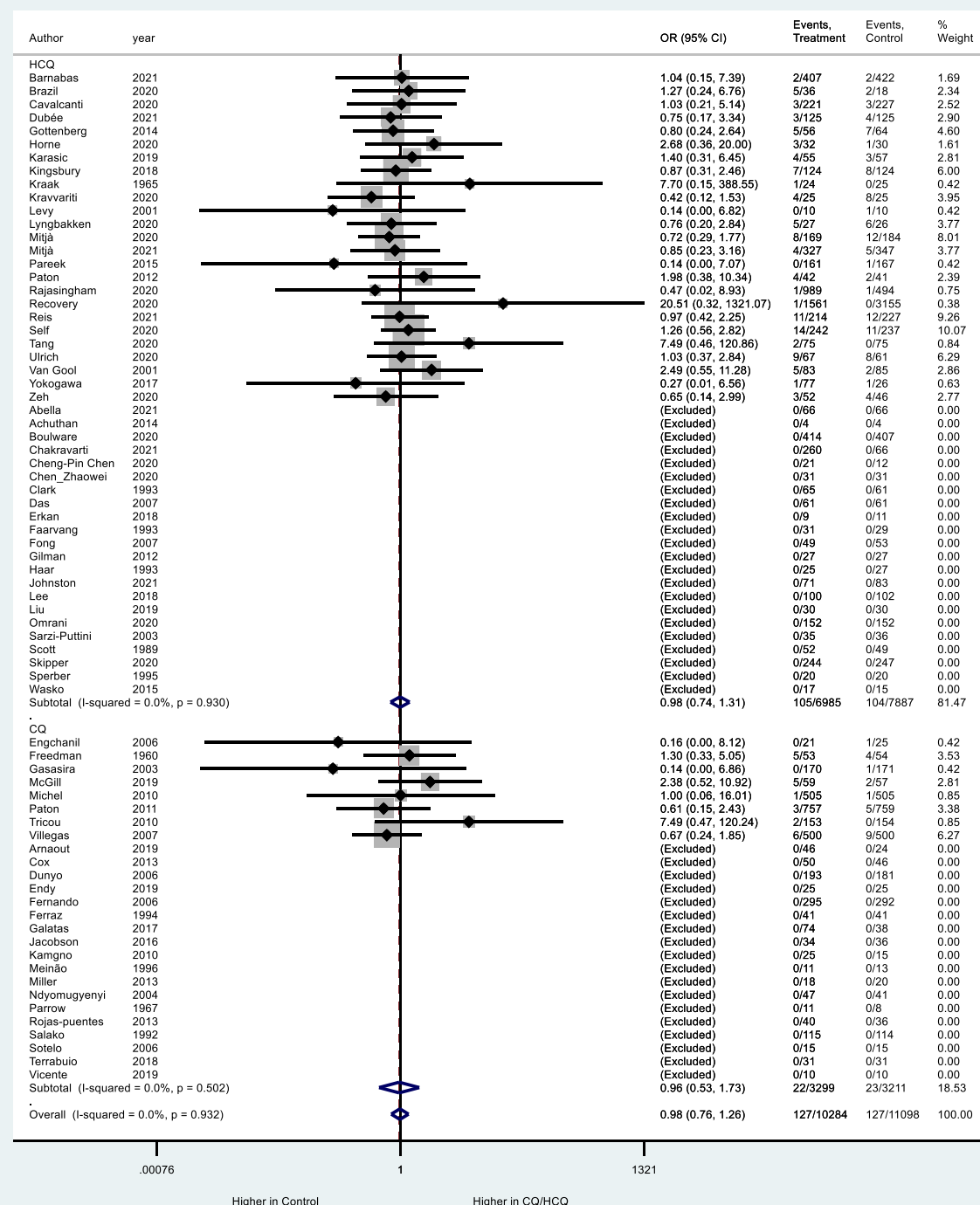


Fig. 3 Meta-analysis for frequency of serious adverse events. Subgroup analysis according to the type of intervention. CQ, chloroquine; HCQ, hydroxychloroquine. Peto's method was adopted and studies with both-armed zero-event were excluded from the analysis. Significance test(s) of OR = 1, overall, $z = 0.16$, $p = 0.872$

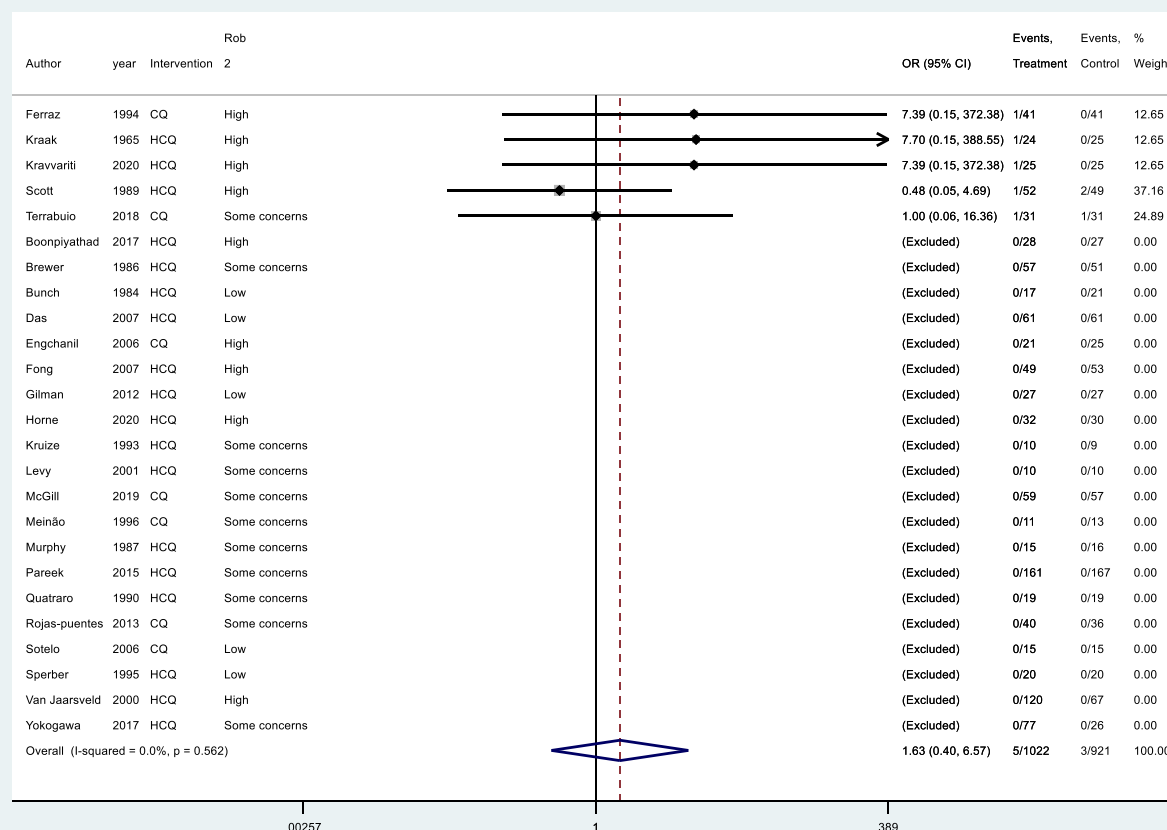


Fig. 4 Meta-analysis for frequency of retinopathy. CQ, chloroquine; HCQ, hydroxychloroquine. Peto's method was adopted and studies with both-armed zero-event were excluded from the analysis. Significance test(s) of OR = 1, $z = 0.69$, $p = 0.492$

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 [136]. Golder and colleagues found that the median percentage of published documents with AE information was 46% compared with 95% in the corresponding unpublished documents [136]. 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 outcomes 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 [137], 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's 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.

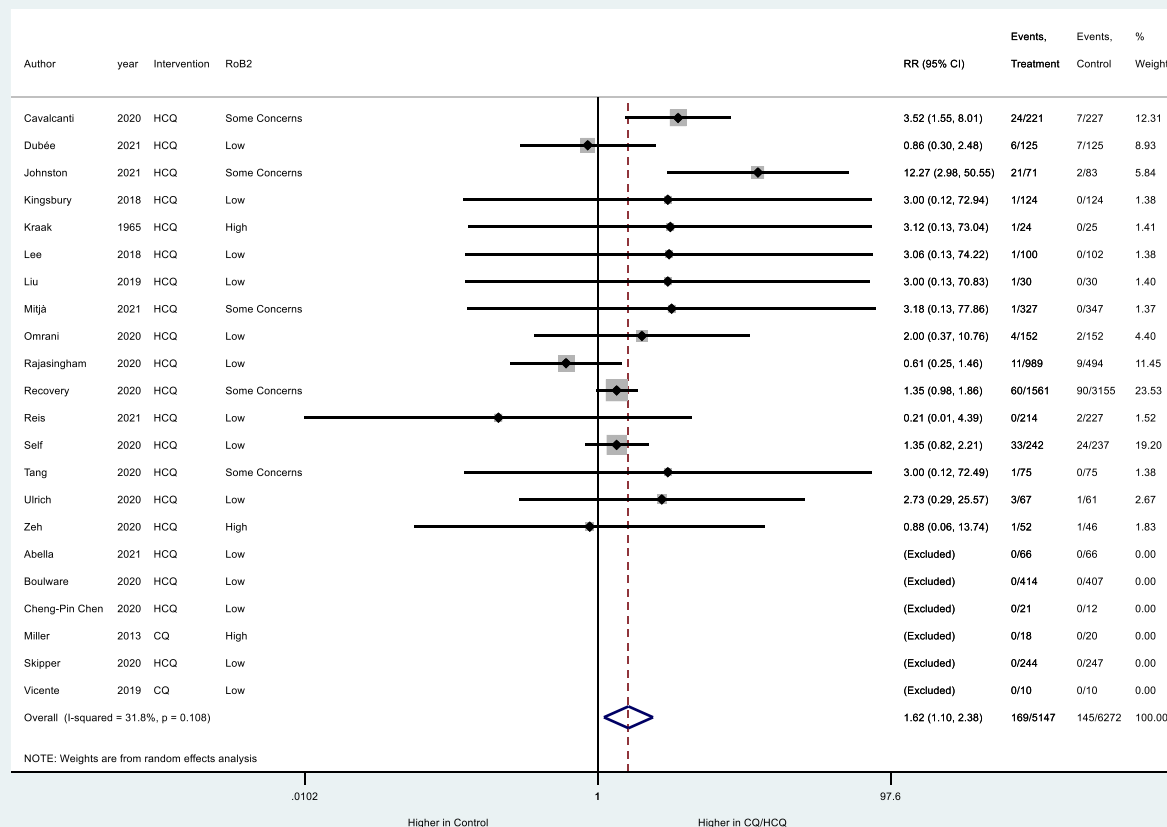


Fig. 5 Meta-analysis for frequency of cardiac complications. Studies with both-armed zero-event were excluded from the analysis. Significance test(s) of $RR = 1$, $z = 2.60$, $p = 0.009$

Conclusion

In conclusion, from the findings of this systematic review, CQ and HCQ probably do not increase the frequency of SAE from RCTs on malarial and non-malarial conditions. However, they may increase cardiac complications in patients with COVID-19. Due to imprecision and bias in the measurement of the outcomes, no clear effect on the incidence of retinopathy was 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.

Supplementary Information

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Additional file 1.

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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-analyses. 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 the quality of evidence. All authors critically revised the manuscript and approved its final version.

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Availability of data and materials

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

Declarations

Consent of publication

Not applicable.

Ethics approval and consent to participate

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

Competing interests

The authors have no conflicts of interest to declare.

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Supplementary File

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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1. Meta-analyses of secondary outcomes

Fig. I Meta-analysis of total adverse events. Subgroup analysis according to type of intervention. CQ: Chloroquine, HCQ: Hydroxychloroquine.

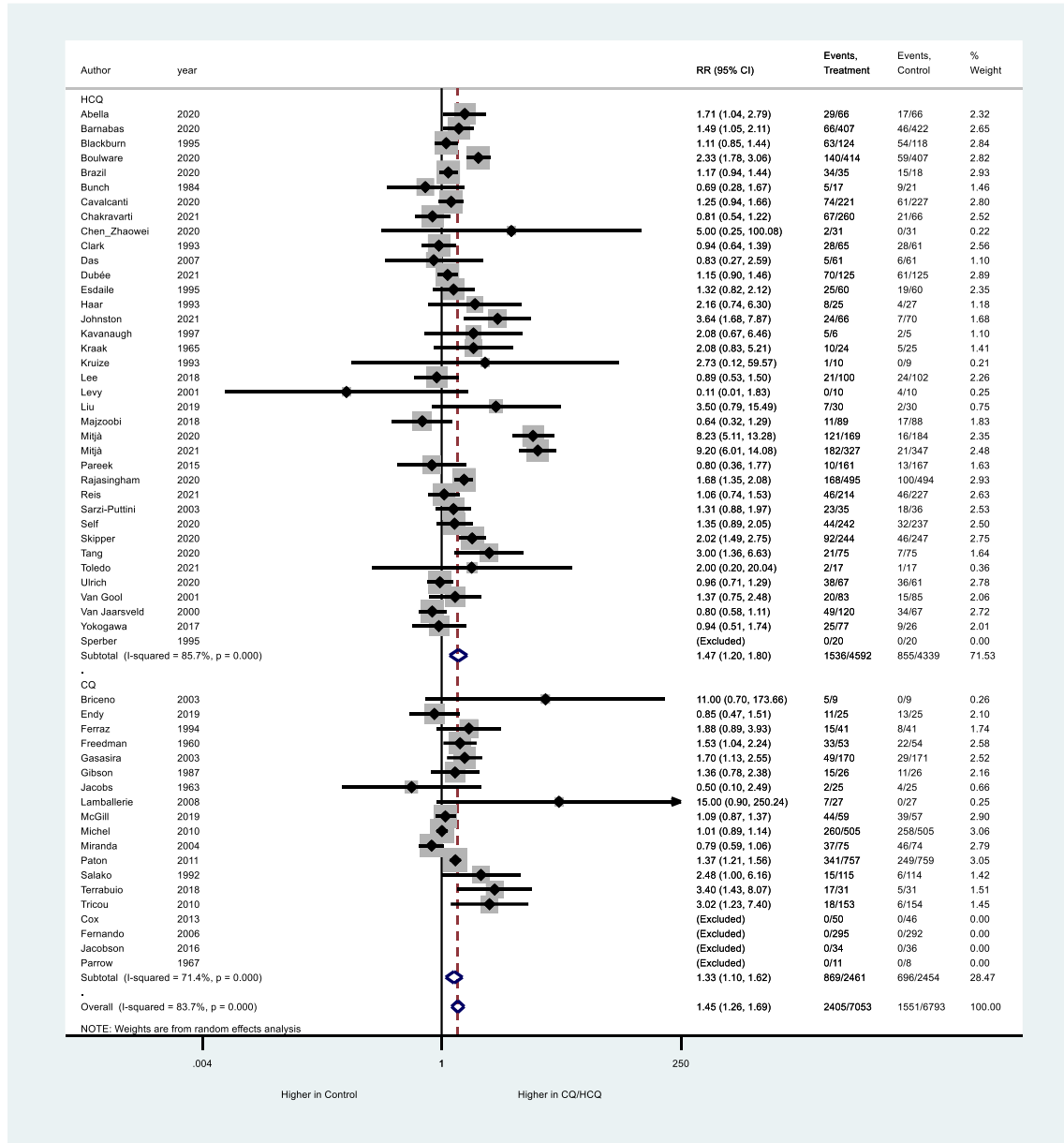


Fig. II Meta-analysis of withdrawal due to any adverse event. Subgroup analysis according to type of intervention. CQ: Chloroquine, HCQ: Hydroxychloroquine. Significance test(s) of RR=1 Overall, $p = 0.003$.

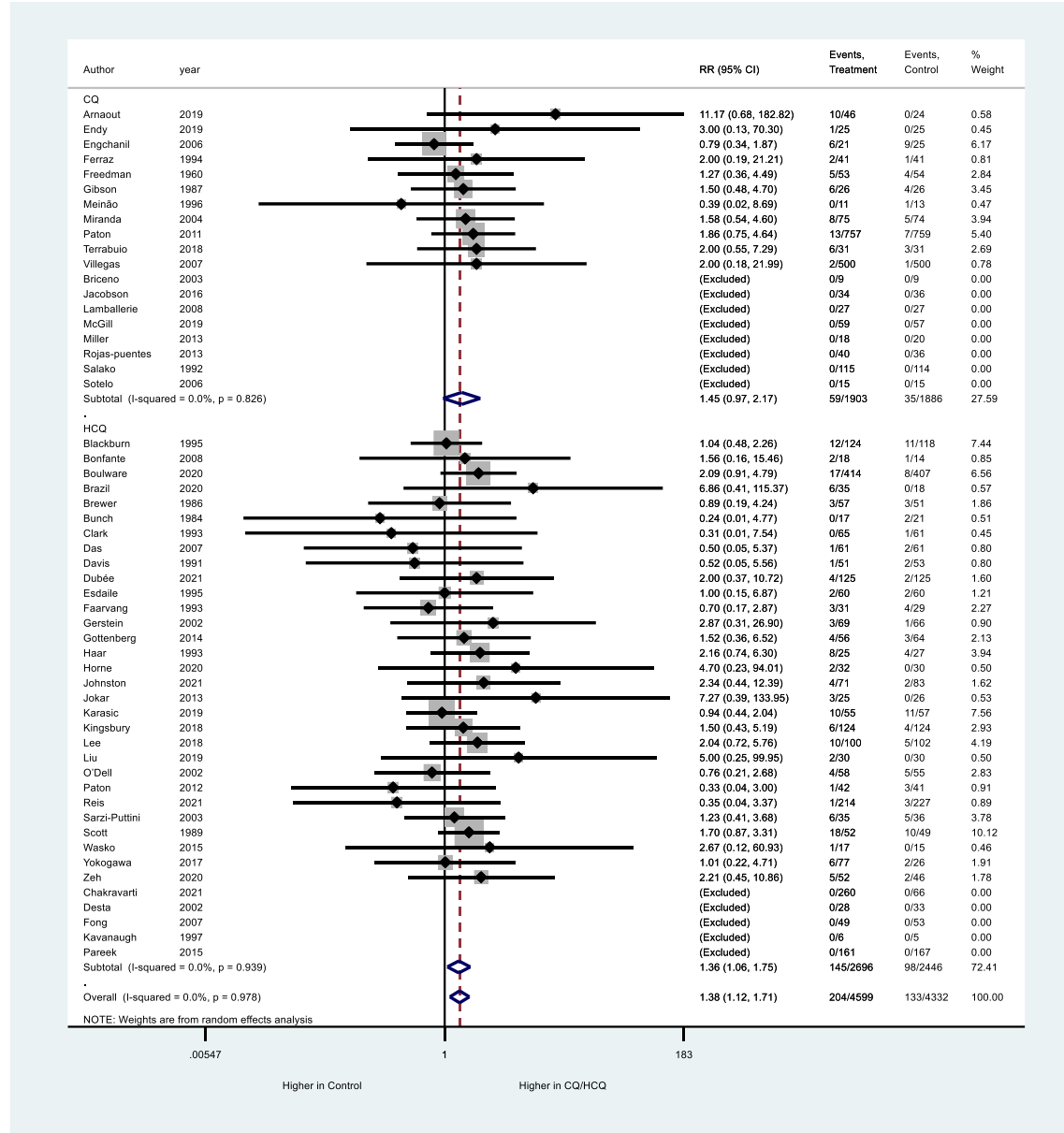


Fig. III Meta-analysis of adverse event nausea and/or vomiting. Subgroup analysis according to type of intervention. CQ: Chloroquine, HCQ: Hydroxychloroquine.

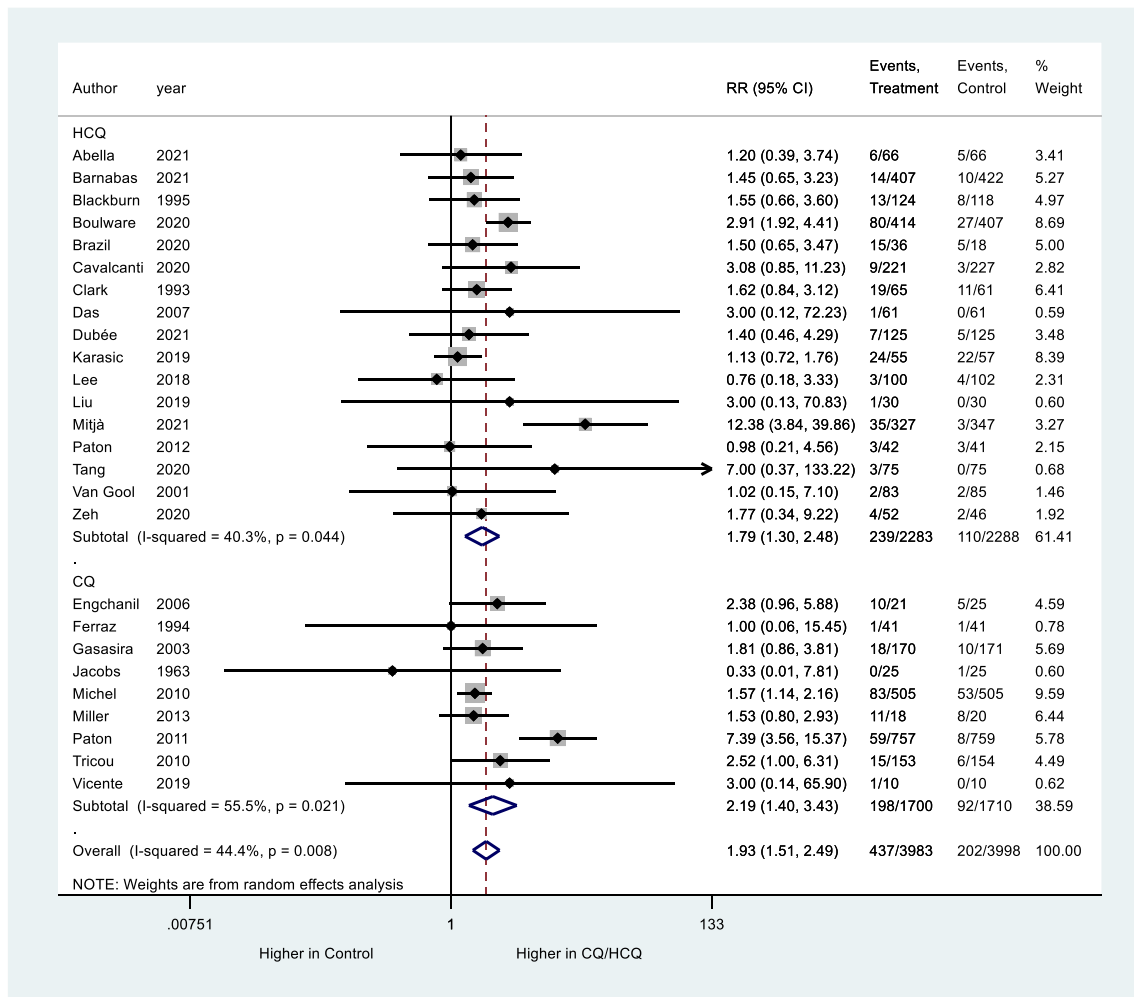


Fig. IV Meta-analysis of adverse event diarrhea. Subgroup analysis according to type of intervention. CQ: Chloroquine, HCQ: Hydroxychloroquine.

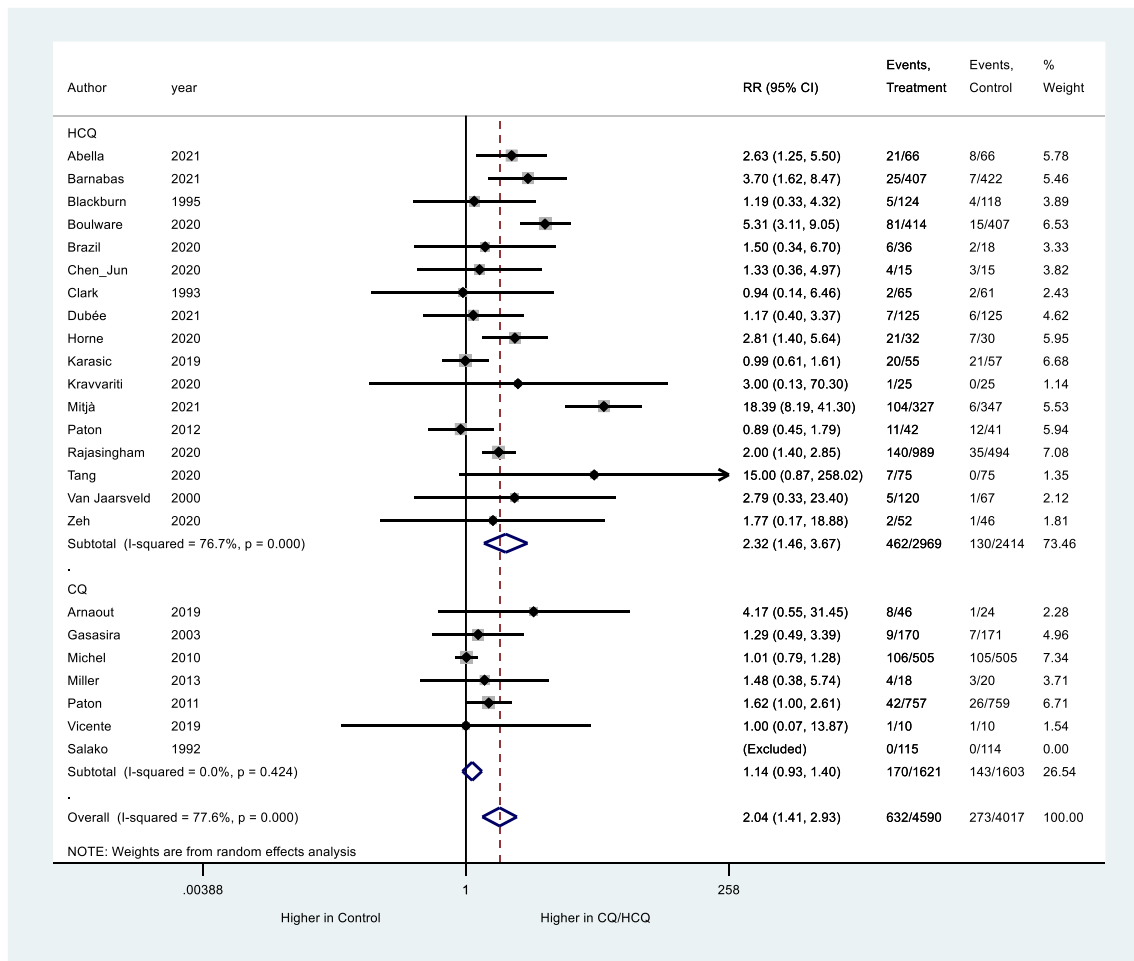


Fig. V Meta-analysis of adverse events of dermatology affections. Subgroup analysis according to type of intervention. CQ: Chloroquine, HCQ: Hydroxychloroquine.

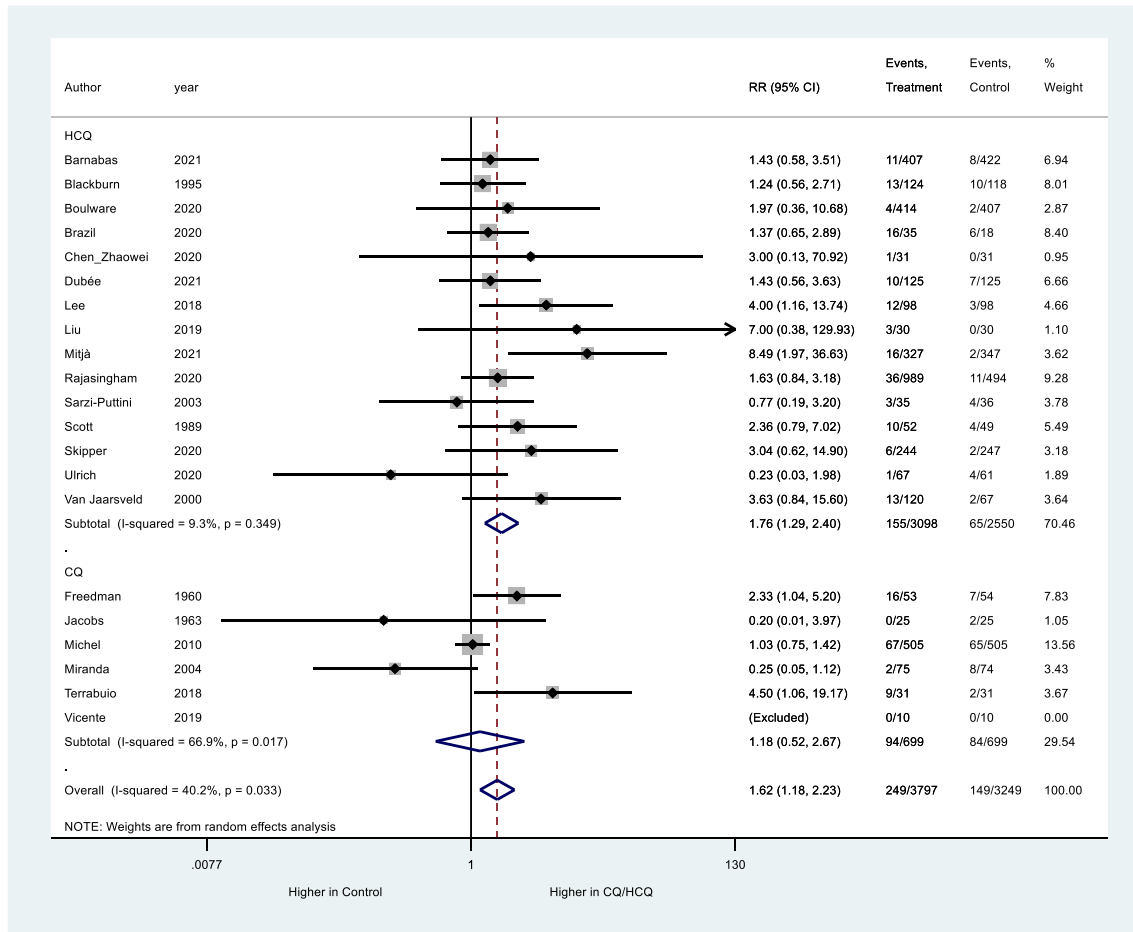


Fig. VI Meta-analysis of adverse event visual complaints. Subgroup analysis according to type of intervention. CQ: Chloroquine, HCQ: Hydroxychloroquine.

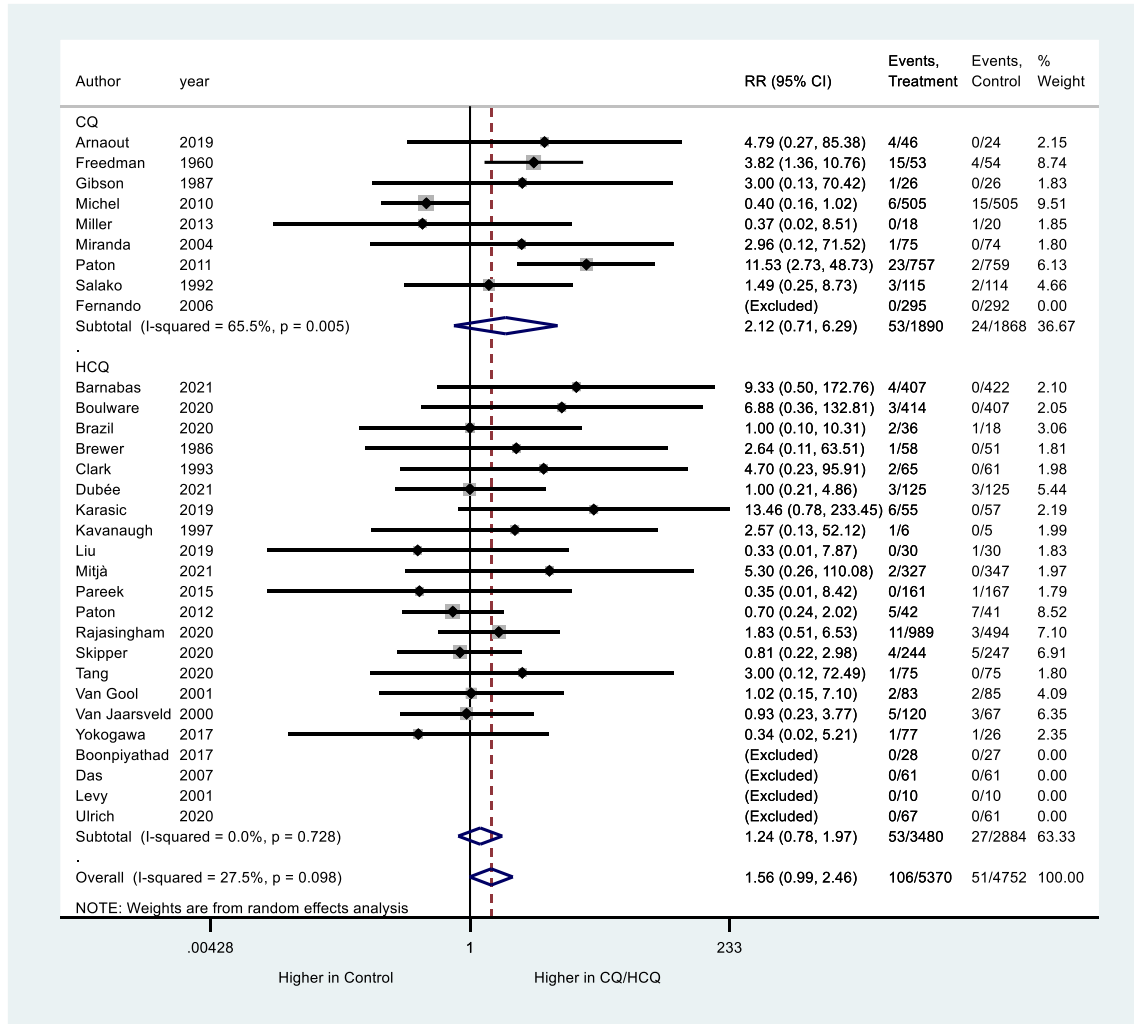


Fig. VII Meta-analysis of adverse event headache. Subgroup analysis according to type of intervention. CQ: Chloroquine, HCQ: Hydroxychloroquine.

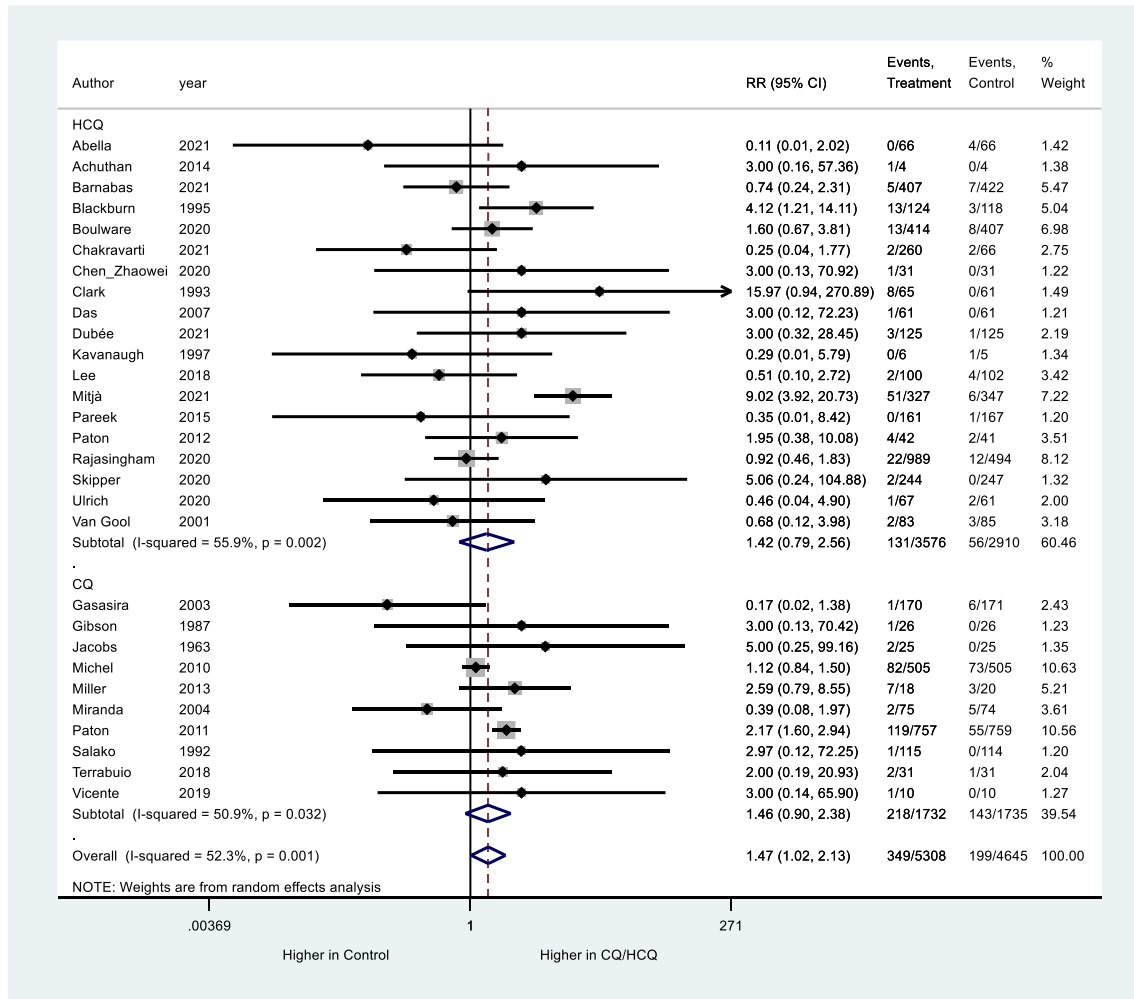
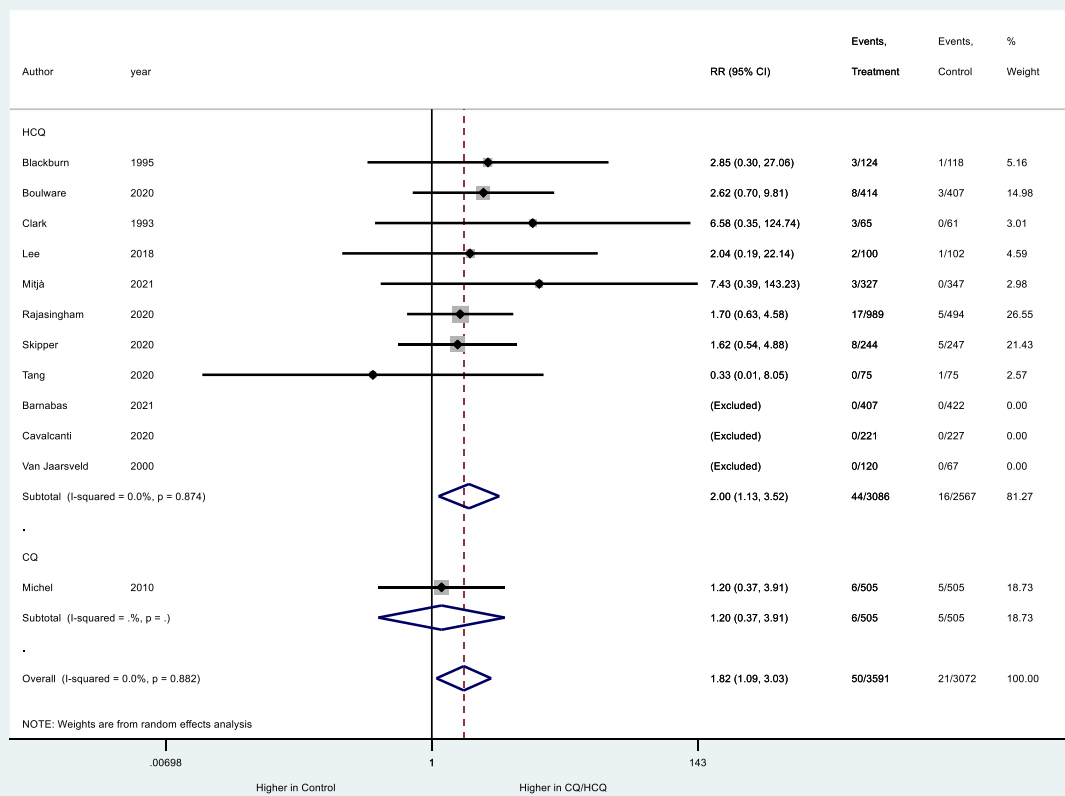


Fig. VIII Meta-analysis of adverse event auditory symptoms. Subgroup analysis according to type of intervention. CQ: Chloroquine, HCQ: Hydroxychloroquine



2. Analyses by subgroups – Serious Adverse Events

Fig. IX Meta-analysis of serious adverse events. Subgroup analysis according to the disease.

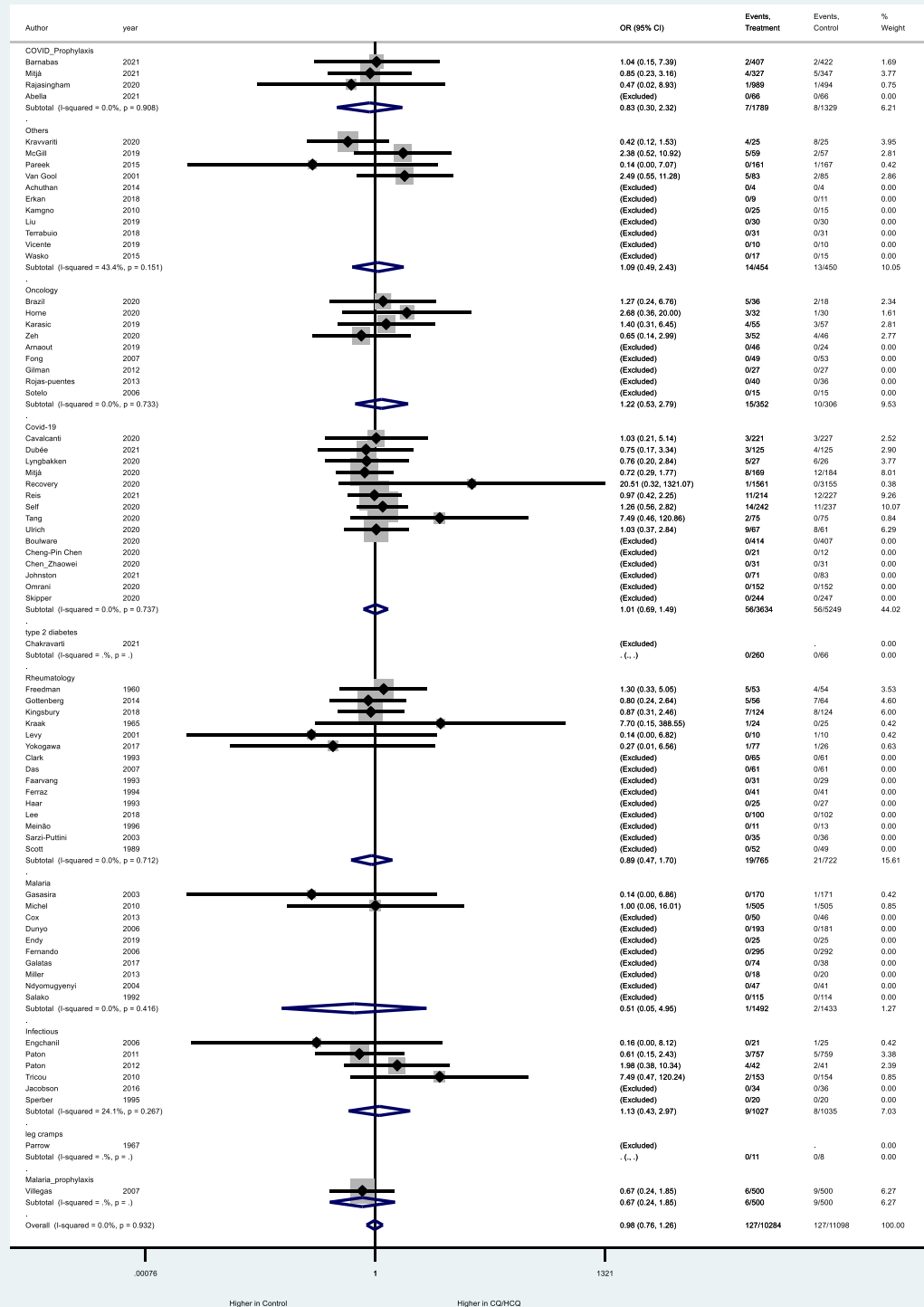


Fig. X Meta-analysis of serious adverse events. Subgroup analysis according to the time of treatment. No: prophylaxis and acute conditions which time of treatment was ≤ 4 weeks. Yes: chronic conditions (> 4 weeks).

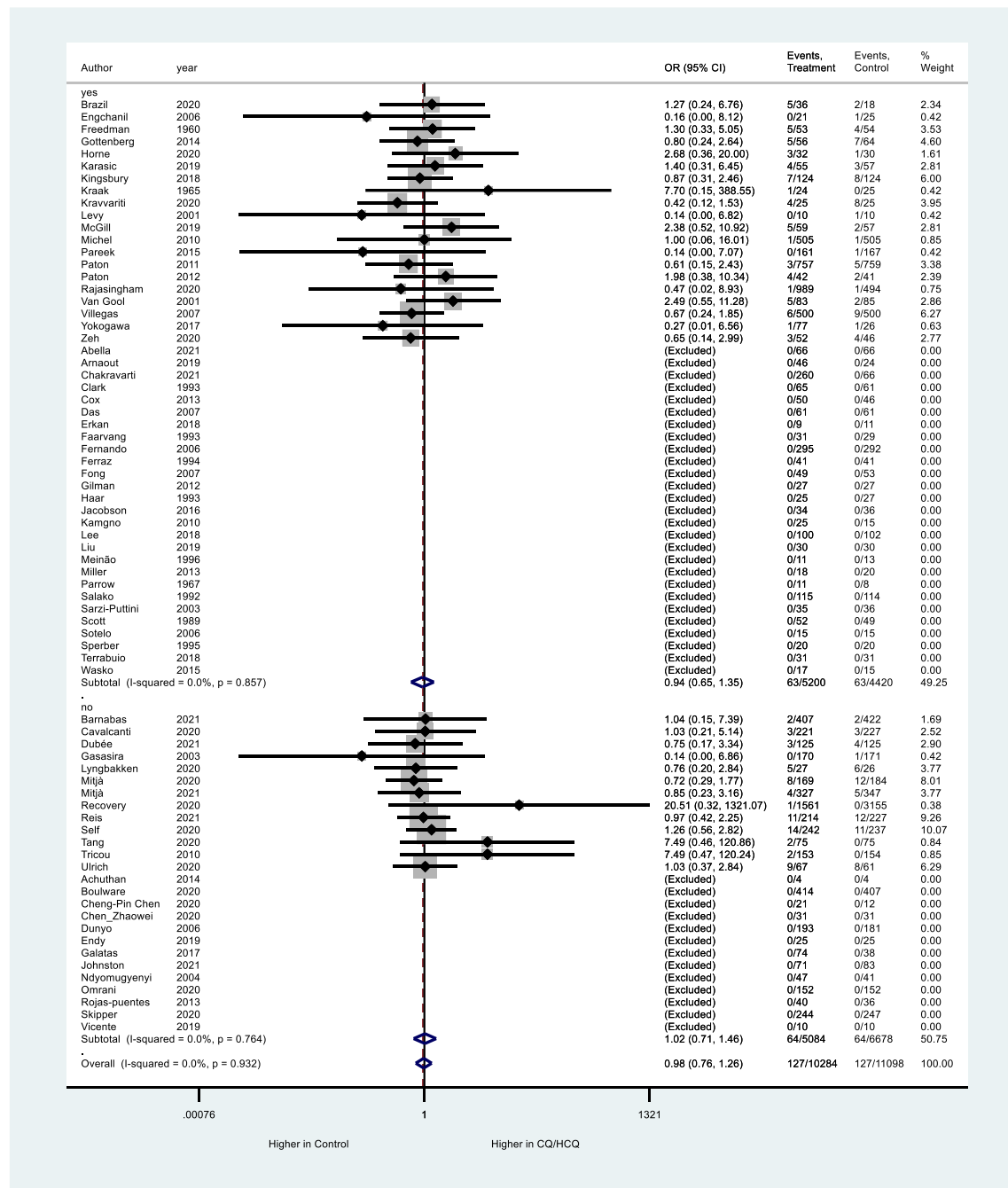


Fig. XI Meta-analysis of serious adverse events. Subgroup analysis according to the dose of the intervention. Yes: daily dose ≥ 500 mg for chloroquine and ≥ 400 mg for hydroxychloroquine. No: daily dose < 500 mg for chloroquine and < 400 mg for hydroxychloroquine.

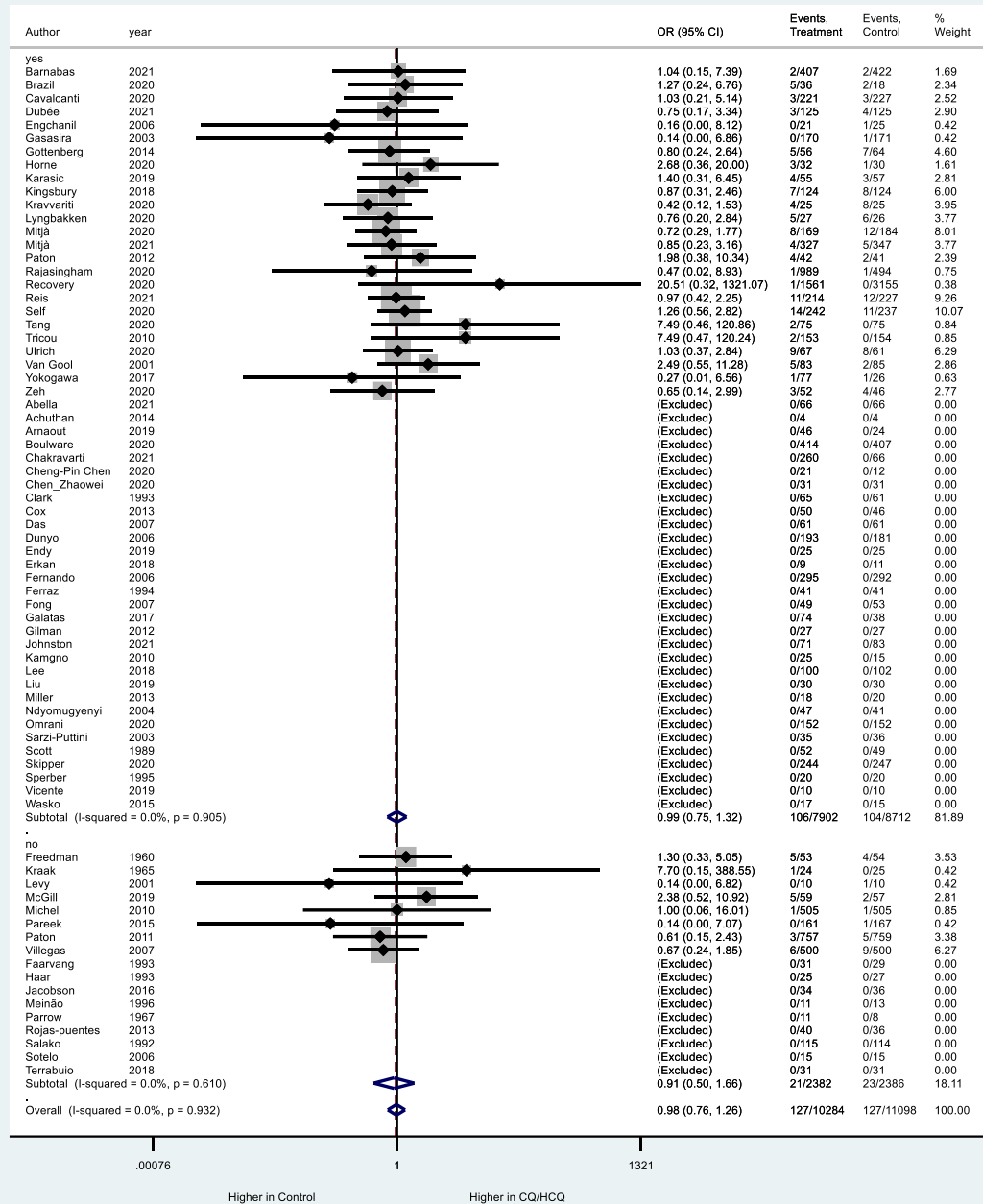
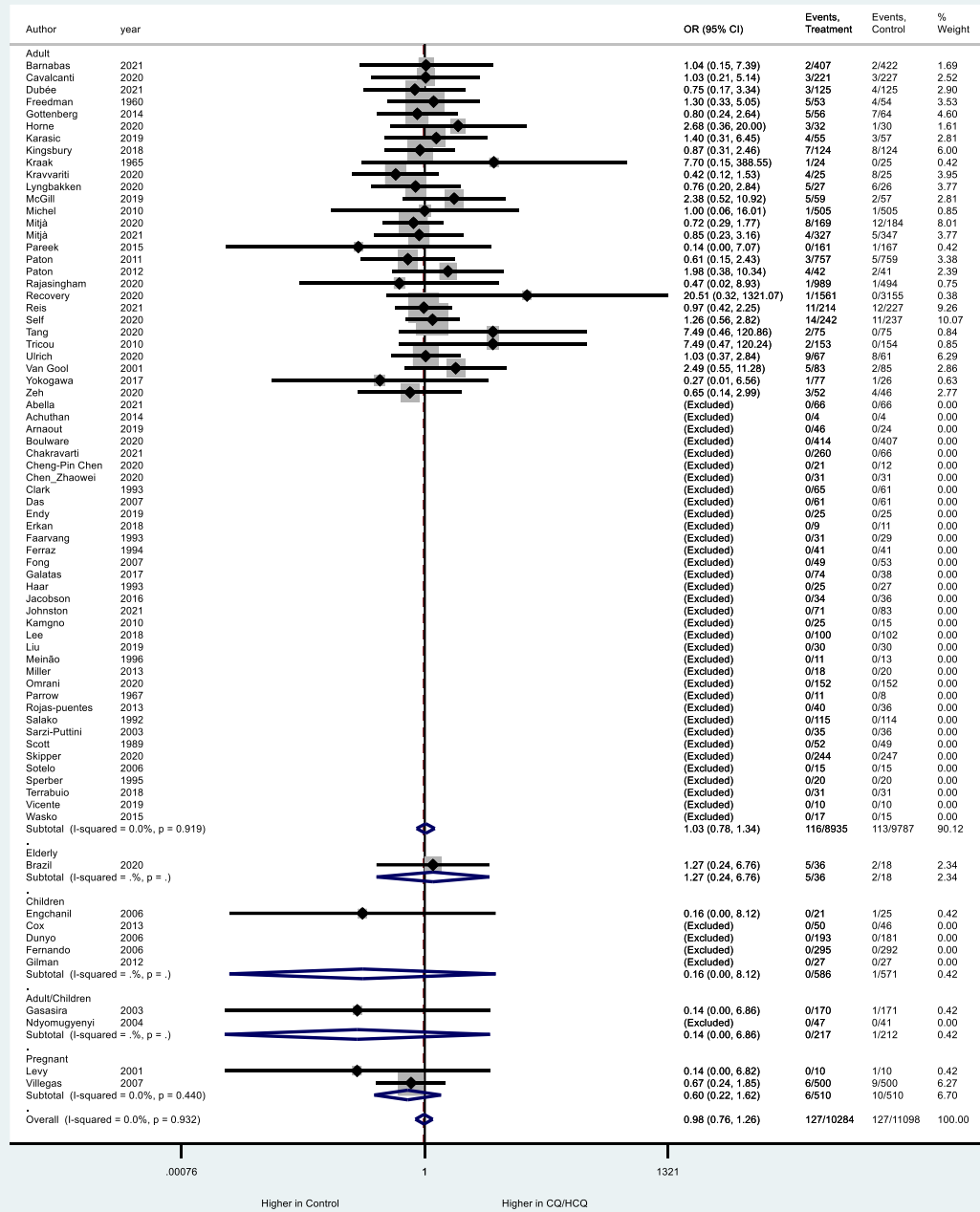


Fig. XII Meta-analysis of serious adverse events. Subgroup analysis according to the studied population: adult, children or pregnant



3. Sensitivity Analyses - Serious Adverse Events (SAE)

Fig. XIII Meta-analysis of serious adverse events. Sensitivity analysis according to risk of bias (RoB 2).

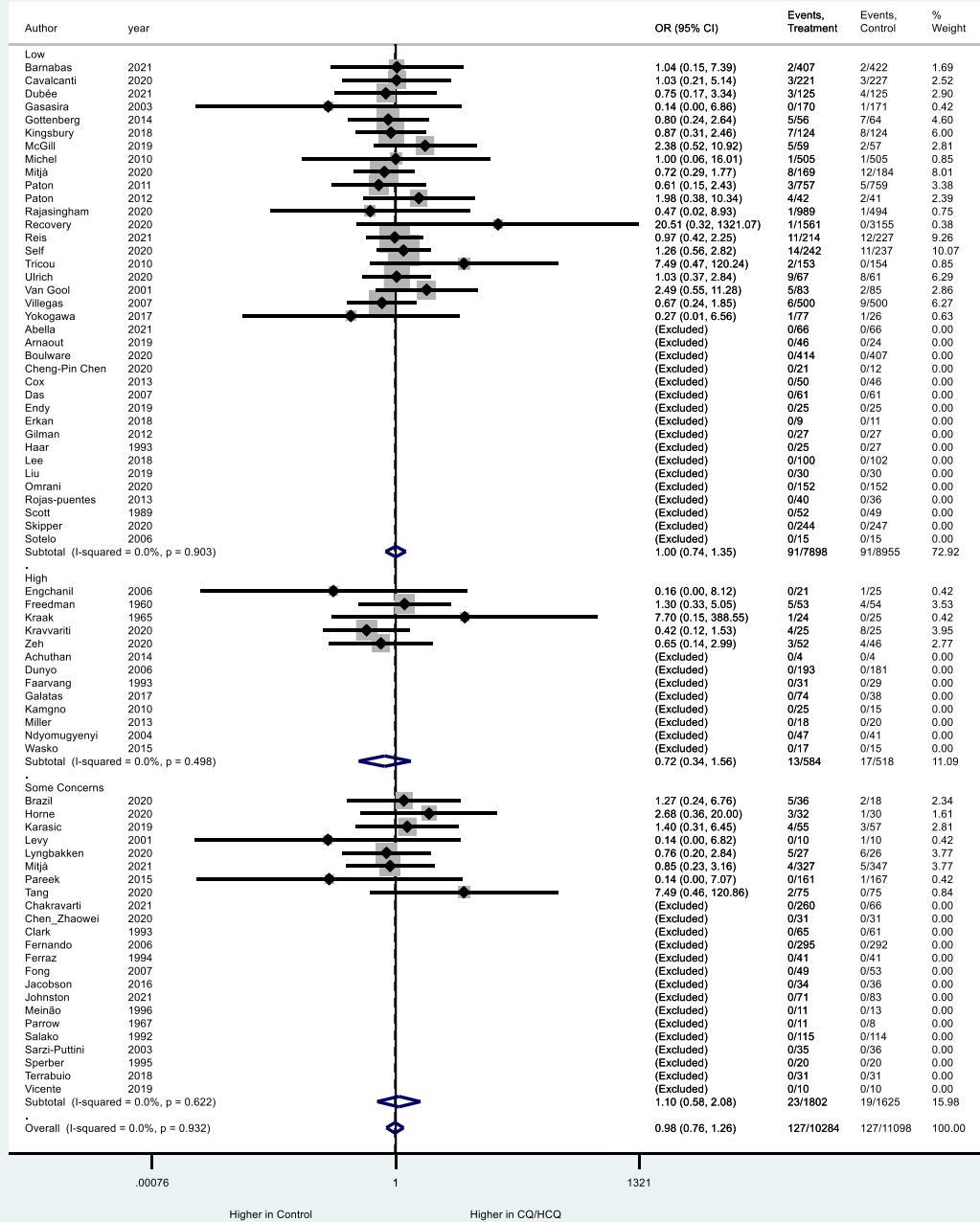


Fig. XIV Meta-analysis of serious adverse events. Sensitivity analysis according to blind of participants and personnel.

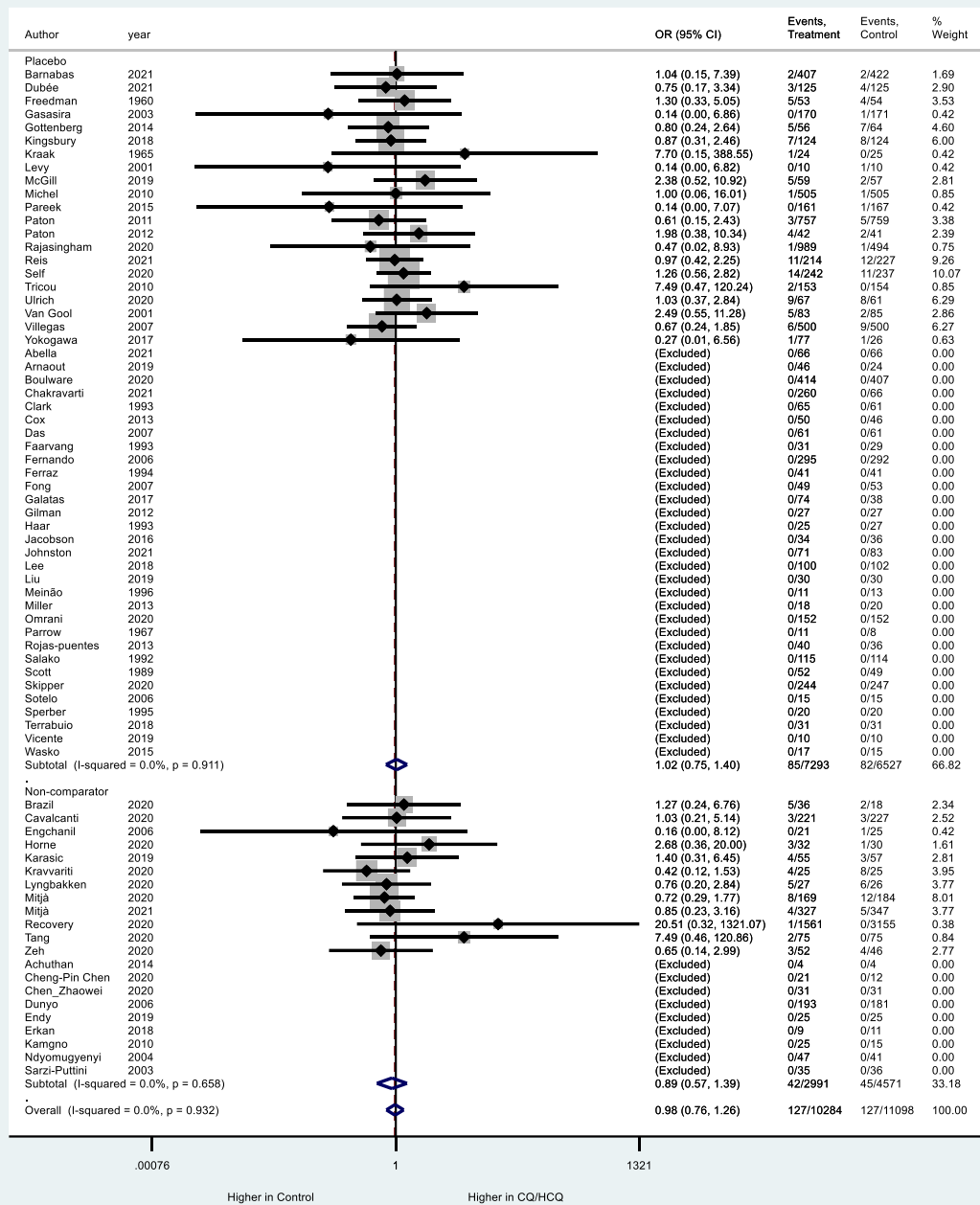


Fig. XV Meta-analysis of serious adverse events. Sensitivity analysis according to sample size: Yes: ≥ 100 participants. No: < 100 participants.

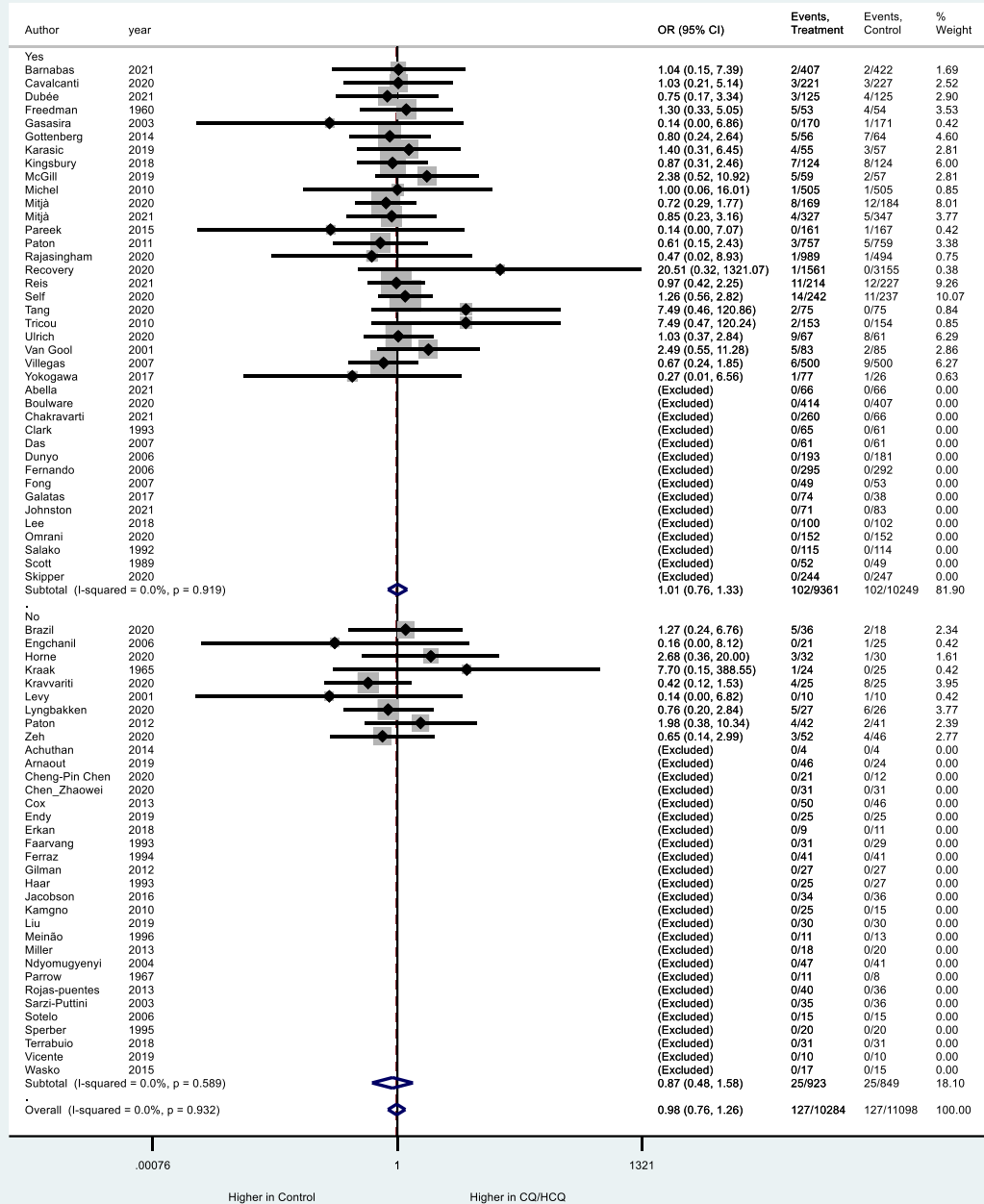
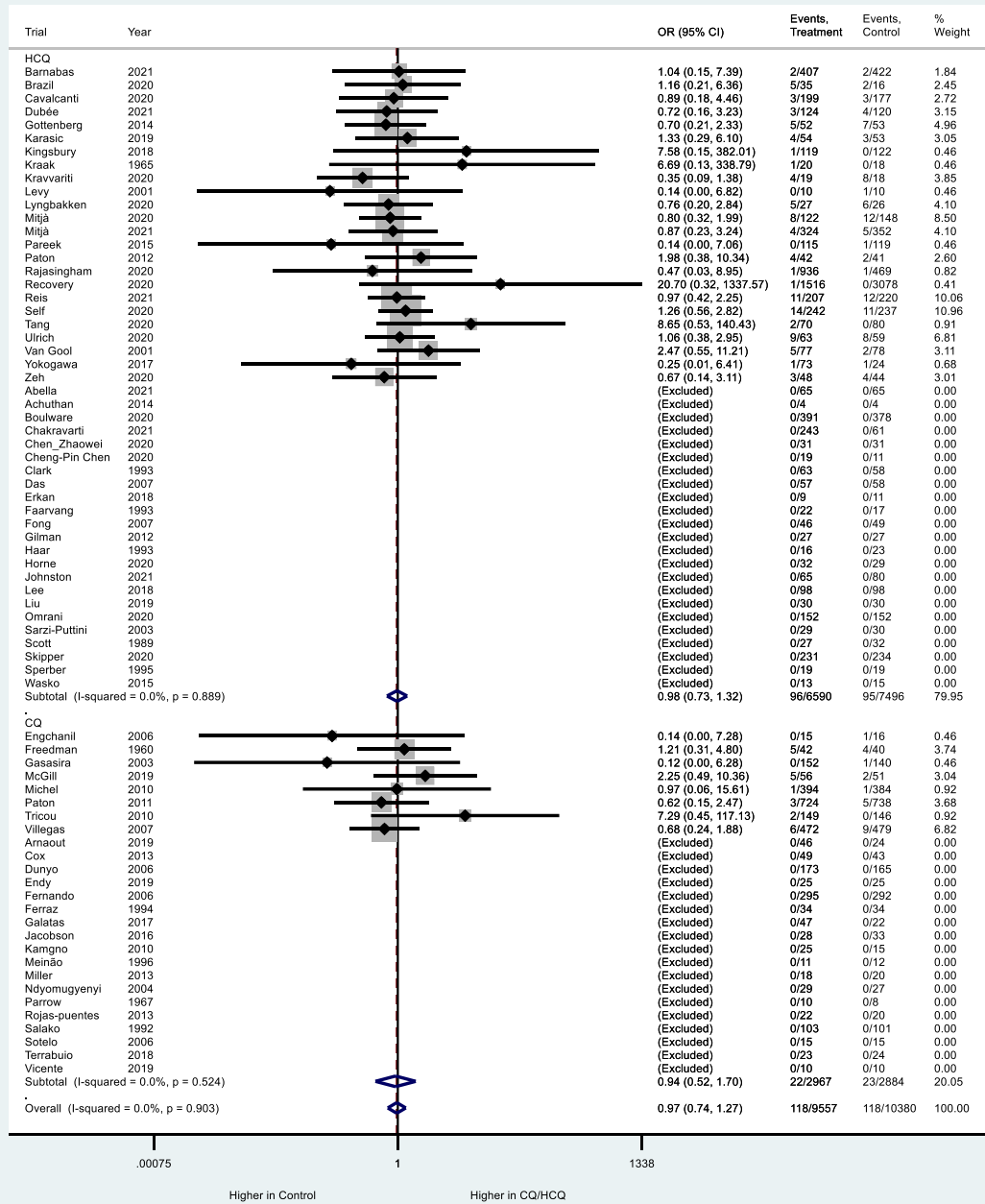
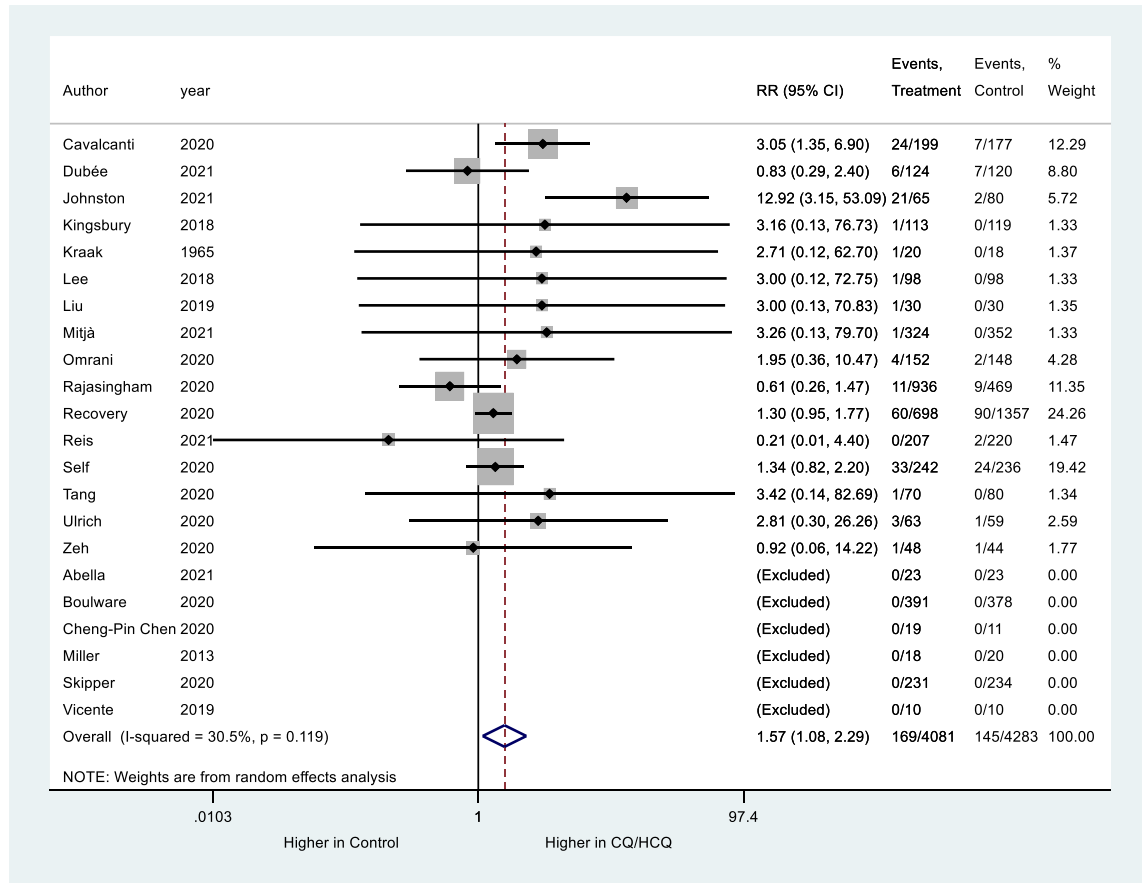


Fig. XVI Meta-analysis of serious adverse events. Sensitivity analysis per protocol.

4. Sensitivity Analyses - Cardiac Complications

Fig. XVII Meta-analysis of cardiac complications. Sensitivity analysis per protocol.



5. Risk of bias (RoB 2)

Fig. XVIII Risk of bias of Retinopathy

Studies with intention-to-treat		Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	Randomization process	Deviations from intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall	
		1	Boonpiyathad 2017	HCQ	Placebo	Retinopathy	0	?	?	?	?	+	+	Low risk
		2	Brewer 1986	HCQ	Placebo	Retinopathy	0	+	+	?	?	+	?	Some concerns
		3	Bunch 1984	HCQ	Placebo	Retinopathy	0	+	+	+	+	+	+	Low risk
		4	Das 2007	HCQ	Placebo	Retinopathy	0	+	+	+	+	+	+	Low risk
		5	Engchanil 2006	CQ	No comparator	Retinopathy	0	+	?	?	?	+	+	Low risk
		6	Ferraz 1994	CQ	Placebo	Retinopathy	0,1265	+	+	+	?	+	+	Low risk
		7	Fong 2007	HCQ	Placebo	Retinopathy	0	?	+	+	+	+	+	Low risk
		8	Gilman 2012	HCQ	Placebo	Retinopathy	0	+	+	+	+	+	+	Low risk
		9	Horne 2020	HCQ	No comparator	Retinopathy	0	+	?	?	+	?	+	Low risk
		10	Kraak 1965	HCQ	Placebo	Retinopathy	0,1265	?	+	?	+	?	+	Low risk
		11	Kravvariti 2020	HCQ	No comparator	Retinopathy	0,1265	+	?	?	?	+	+	Low risk
		12	Kruize 1993	HCQ	Placebo	Retinopathy	0	?	+	+	?	+	+	Low risk
		13	Levy 2001	HCQ	Placebo	Retinopathy	0	?	+	+	+	+	+	Low risk
		14	McGill 2019	CQ	Placebo	Retinopathy	0	+	+	+	?	+	+	Low risk
		15	Meinão 1996	CQ	Placebo	Retinopathy	0	?	+	+	+	+	+	Low risk
		16	Murphy 1987	HCQ	Placebo	Retinopathy	0	?	+	?	+	+	+	Low risk
		17	Pareek 2015	HCQ	Placebo	Retinopathy	0	+	+	?	+	+	+	Low risk
		18	Quatraro 1990	HCQ	Placebo	Retinopathy	0	+	+	+	?	+	+	Low risk
		19	Rojas Puentes 2011	CQ	Placebo	Retinopathy	0	+	+	+	?	+	+	Low risk
		20	Scott 1989	HCQ	Placebo	Retinopathy	0,3716	+	+	?	?	+	+	Low risk
		21	Sotelo 2006	CQ	Placebo	Retinopathy	0	+	+	+	+	+	+	Low risk
		22	Sperber 1995	HCQ	Placebo	Retinopathy	0	+	+	+	+	+	+	Low risk
		23	Terrabuio 2018	CQ	Placebo	Retinopathy	0,2489	?	+	?	+	+	+	Low risk
		24	Van Jaarsveld 2000	HCQ	No comparator	Retinopathy	0	+	?	?	+	?	+	Low risk
		25	Yokogawa 2017	HCQ	Placebo	Retinopathy	0	+	+	?	+	+	+	Low risk

6. Risk of bias (RoB 2)

Fig. XIX Risk of bias of Cardiac complication

Studies with intention-to- treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	Randomization process	Deviations from intended interven	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall	
		1 Abella 2021	HCQ	Placebo	Cardiovascular	0	+	+	+	+	+	+	Low risk
		2 Boulware 2020	HCQ	Placebo	Cardiovascular	0	+	+	+	+	+	+	Low risk
		3 Cavalcanti 2020	HCQ	Non-CQ/HCQ	Cardiovascular	0,1185	+	?	?	+	+	?	Some concerns
		4 Cheng Pin 2020	HCQ	Placebo	Cardiovascular	0	+	+	+	+	+	+	Low risk
		5 Dub��e 2021	HCQ	Placebo	Cardiovascular	0,0813	+	+	+	+	+	+	Low risk
		6 Johnston 2021	HCQ	Placebo	Cardiovascular	0,0506	?	+	?	+	+	?	Some concerns
		7 Kingsbury 2018	HCQ	Placebo	Cardiovascular	0,0112	+	+	+	+	+	+	Low risk
		8 Kraak 1965	HCQ	Placebo	Cardiovascular	0,0114	+	+	?	+	+	+	Low risk
		9 Lee 2018	HCQ	Placebo	Cardiovascular	0,0112	+	+	+	+	+	+	Low risk
		10 Liu 2019	HCQ	Placebo	Cardiovascular	0,0114	+	+	+	+	+	+	Low risk
		11 Miller 2013	CQ	Placebo	Cardiovascular	0	+	+	+	+	+	+	Low risk
		12 Mitj�� 2021	HCQ	Non-CQ/HCQ	Cardiovascular	0,0238	?	?	?	+	+	?	Some concerns
		13 Omrani 2020	HCQ	Placebo	Cardiovascular	0,0373	+	+	+	+	+	+	Low risk
		14 Rajasingham 2020	HCQ	Placebo	Cardiovascular	0,092	+	+	+	+	+	+	Low risk
		15 Recovery 2020	HCQ	Non-CQ/HCQ	Cardiovascular	0,2811	+	?	?	+	?	?	Some concerns
		16 Reis 2021	HCQ	Placebo	Cardiovascular	0,0123	+	+	+	+	+	+	Low risk
		17 Self 2020	HCQ	Placebo	Cardiovascular	0,2099	+	+	+	+	+	+	Low risk
		18 Skipper 2020	HCQ	Placebo	Cardiovascular	0	+	+	+	+	+	+	Low risk
		19 Tang 2020	HCQ	Non-CQ/HCQ	Cardiovascular	0,0112	?	?	+	+	?	?	Some concerns
		20 Ulrich 2020	HCQ	Placebo	Cardiovascular	0,022	+	+	+	+	+	+	Low risk
		21 Vicente 2019	CQ	Placebo	Cardiovascular	0	?	+	+	+	+	?	Some concerns
		22 Zeh 2020	HCQ	Non-CQ/HCQ	Cardiovascular	0,0149	?	?	+	+	+	+	Low risk

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10. Search Strategies - 11/April/2021

PubMed

#1 "Hydroxychloroquine"[Mesh] OR (Oxychlorochin) OR (Oxychloroquine) OR (Hydroxychlorochin) OR (Plaquenil) OR (Hydroxychloroquine Sulfate) OR (Hydroxychloroquine Sulfate (1:1) Salt)

2 "Chloroquine"[Mesh] OR (Chlorochin) OR (Chingamin) OR (Khingamin) OR (Nivaquine) OR (Chloroquine Sulfate) OR (Sulfate, Chloroquine) OR (Chloroquine Sulphate) OR (Sulphate, Chloroquine) OR (Aralen) OR (Arequin OR (Arequin) OR (Arechine)

#3 "chloroquine diphosphate" [Supplementary Concept] OR (chingamin phosphate) OR (unspecified phosphate of chloroquine diphosphate) OR (delagil) OR (khingamin phosphate) OR (arechin) OR (chloroquine phosphate) OR (Resochin) OR (chloroquine diphosphate, (+-)-isomer) OR (chloroquine diphosphate, (-)-isomer) OR (chloroquine bis(dihydrogenphosphate) dihydrate) OR (chloroquine diphosphate, (+)-isomer)

*4 randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh]))

***sensitivity- and precision-maximizing version (2008 revision); PubMed format – Cochrane**

((("chloroquine diphosphate" [Supplementary Concept] OR (chingamin phosphate) OR (unspecified phosphate of chloroquine diphosphate) OR (delagil) OR (khingamin phosphate) OR (arechin) OR (chloroquine phosphate) OR (Resochin) OR (chloroquine diphosphate, (+-)-isomer) OR (chloroquine diphosphate, (-)-isomer) OR (chloroquine bis(dihydrogenphosphate) dihydrate) OR (chloroquine diphosphate, (+)-isomer)) OR ("Chloroquine"[Mesh] OR (Chlorochin) OR (Chingamin) OR (Khingamin) OR (Nivaquine) OR (Chloroquine Sulfate) OR (Sulfate, Chloroquine) OR (Chloroquine Sulphate) OR (Sulphate, Chloroquine) OR (Aralen) OR (Arequin) OR (Arequin) OR (Arechine))) OR ("Hydroxychloroquine"[Mesh] OR (Oxychlorochin) OR (Oxychloroquine) OR (Hydroxychlorochin) OR (Plaquenil) OR (Hydroxychloroquine Sulfate) OR (Hydroxychloroquine Sulfate (1:1) Salt))) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh]))))

Total= 1543

EMBASE

'hydroxychloroquine'/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' OR 'chloroquinol' OR 'ercoquin' OR 'hydrochloroquine' OR 'hydrochloroquine' OR 'oxychloroquine' OR 'quensyl' OR 'sn 8137'

'hydroxychloroquine sulfate'/exp OR '1 (7 chloro 4 quinolylamino) 3 diethylamino 2 propanol sulfate' OR '1 (7 chloro 4 quinolylamino) 3 diethylamino 2 propanol sulphate' OR '2 [[4 [(7 chloro 4 quinolyl) amino] pentyl] (ethyl) amino] ethanol sulfate' OR '2 [[4 [(7 chloro 4 quinolyl) amino] pentyl] (ethyl) amino] ethanol sulphate' OR '2 [[4 [(7 chloroquinolin 4 yl) amino] pentyl] (ethyl) amino] ethanol sulfate' OR '2 [[4 [(7 chloroquinolin 4 yl) amino] pentyl] (ethyl) amino] ethanol sulphate' OR '7 chloro

4 (3 diethylamino 2 hydroxypropylamino) quinoline sulfate' OR '7 chloro 4 (3 diethylamino 2 hydroxypropylamino) quinoline sulphate' OR 'dimard' OR 'erquin' OR 'evoquin' OR 'geniquin' OR 'hydroxychloroquine sulphate' OR 'oxiklorin' OR 'oxychloroquine sulfate' OR 'oxychloroquine sulphate' OR 'plaquenil' OR 'plaquenil sulfate' OR 'plaquenil sulphate' OR 'plaquinol' OR 'toremonil' OR 'yuma'

'chloroquine'/exp OR '4 (4 diethylamino 1 methylbutylamino) 7 chlorochinolin diphosphate' OR '4 (4 diethylamino 1 methylbutylamino) 7 chlorochinolin sulfate' OR '4 (4 diethylamino 1 methylbutylamino) 7 chlorochinolin sulphate' 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 'chlorochi' 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 'klorokinofosfat' 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 'resoehen' OR 'resoehene' OR 'resoehin' OR 'resoehin junior' OR 'resoehina' OR 'resoehine' OR 'resoehinon' 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 '7618' OR 'w7618' OR 'win 244' OR 'win244'

Filter

best optimization of sensitivity and specificity*

random*:ab,ti OR placebo*:de,ab,ti OR (double NEXT/1 blind*):ab,ti

*Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association : JMLA. 2006 Jan;94(1):41-7

Total=3726

CENTRAL

Search Name:

Date Run: 20/04/2020 10:37:49

Comment:

ID Search Hits

- #1 MeSH descriptor: [Hydroxychloroquine] explode all trees 302
- #2 'Hydroxychloroquine Sulfate Salt' OR 'Hydroxychloroquine Sulfate' OR 'Plaquenil' OR 'Hydroxychlorochin' OR 'Oxychlorochin' OR 'Oxychloroquine' 104
- #3 MeSH descriptor: [Chloroquine] explode all trees 976
- #4 'Chloroquine Sulphate' OR 'Chloroquine Sulfate' OR 'Sulphate, Chloroquine' OR 'Sulfate, Chloroquine' 35
- #5 #1 OR #2 OR #3 OR #4 1055

BVS (Lilacs, IBECs, Hansenias, Sec Muni SP, Coleciona Sus)

#1 MH:"Hidroxicloroquina" OR (Oxicloroquina) OR MH: D03.633.100.810.050.180.350\$

#2 MH:"Cloroquina" OR MH: D03.633.100.810.050.180\$

#1 OR #2= 156

Trip Database

Hydroxychloroquine, filter controlled trial 199

Chloroquine, filter controlled trial 549

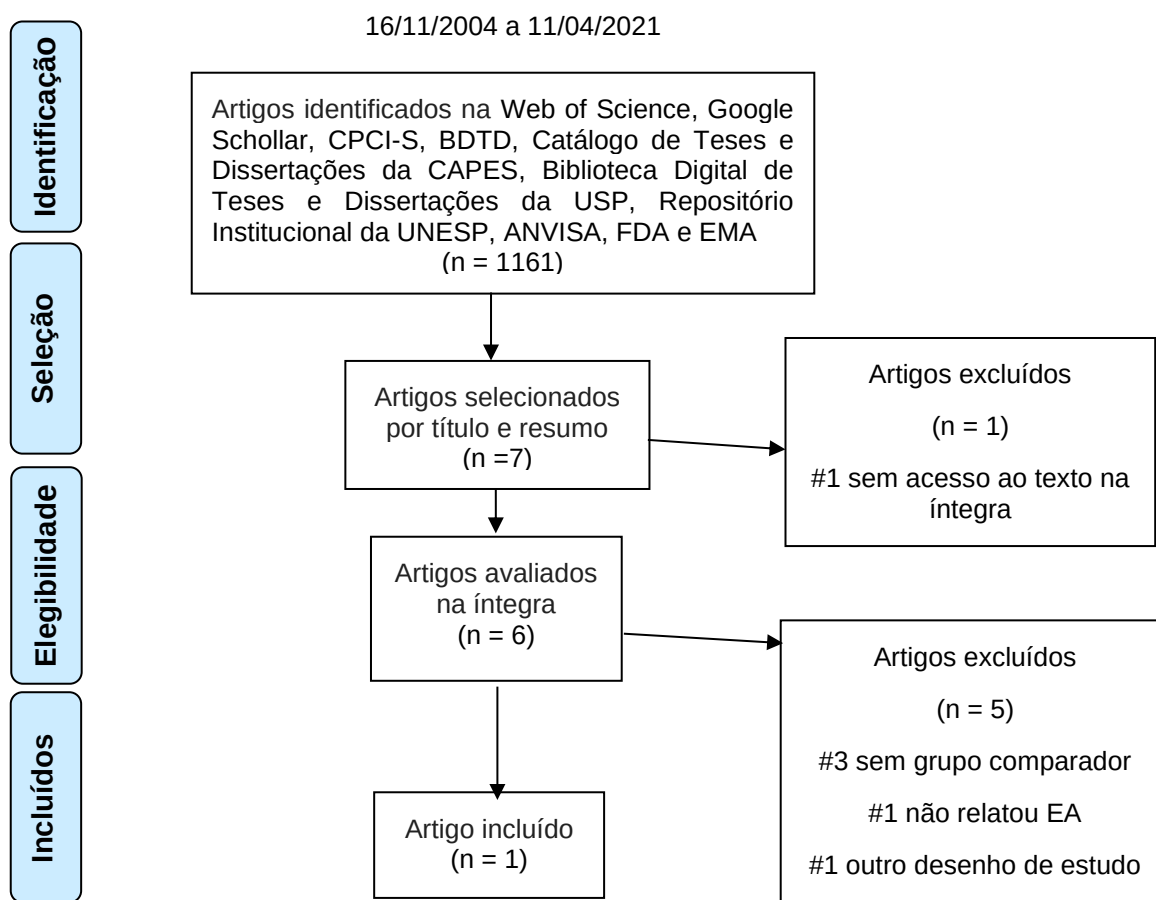
SCOPUS

LL (" Hydroxychloroquine") OR ALL (" Chloroquine ") AND ALL ("randomized controlled trial") AND NOT INDEX (medline) AND (LIMIT-TO (DOCTYPE , "ar"))
Total= 866

Resultados após publicação

As estratégias de busca para estudos não publicados geraram 1161 resultados e após a triagem inicial de títulos e resumos, foram selecionados sete estudos. Seis artigos foram avaliados na íntegra e apenas um deles preencheu os critérios de elegibilidade, conforme Figura 1.

Figura 1 – Fluxograma de seleção dos estudos não publicados



Legendas: CPCI-S= *Conference Proceedings Citation Index – Science*, BDTD= Biblioteca Digital Brasileira de Teses e Dissertações, CAPES= Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, USP= Universidade de São Paulo, UNESP= Universidade Estadual Paulista “Júlio de Mesquita Filho”, ANVISA= Agência Nacional de Vigilância Sanitária, FDA= *Food and Drug Administration*, EMA= *European Medicines Agency*, EA= eventos adversos.

Fonte: elaborado pelo autor (2023)

O estudo selecionado é um ensaio clínico randomizado (ECR) sobre o uso de cloroquina (CQ) e hidroxicloroquina (HCQ) no tratamento da COVID-19, em formato de pré-impressão. Nesse estudo, não houve relato de EAGs, retinopatia ou complicações cardíacas relacionados a CQ e HCQ, impossibilitando a sua comparação com os demais estudos publicados. Contudo, notou-se um maior número de eventos adversos totais nos grupos de CQ e HCQ, em relação ao grupo controle, à semelhança do que foi encontrado nos estudos publicados da nossa revisão (50).

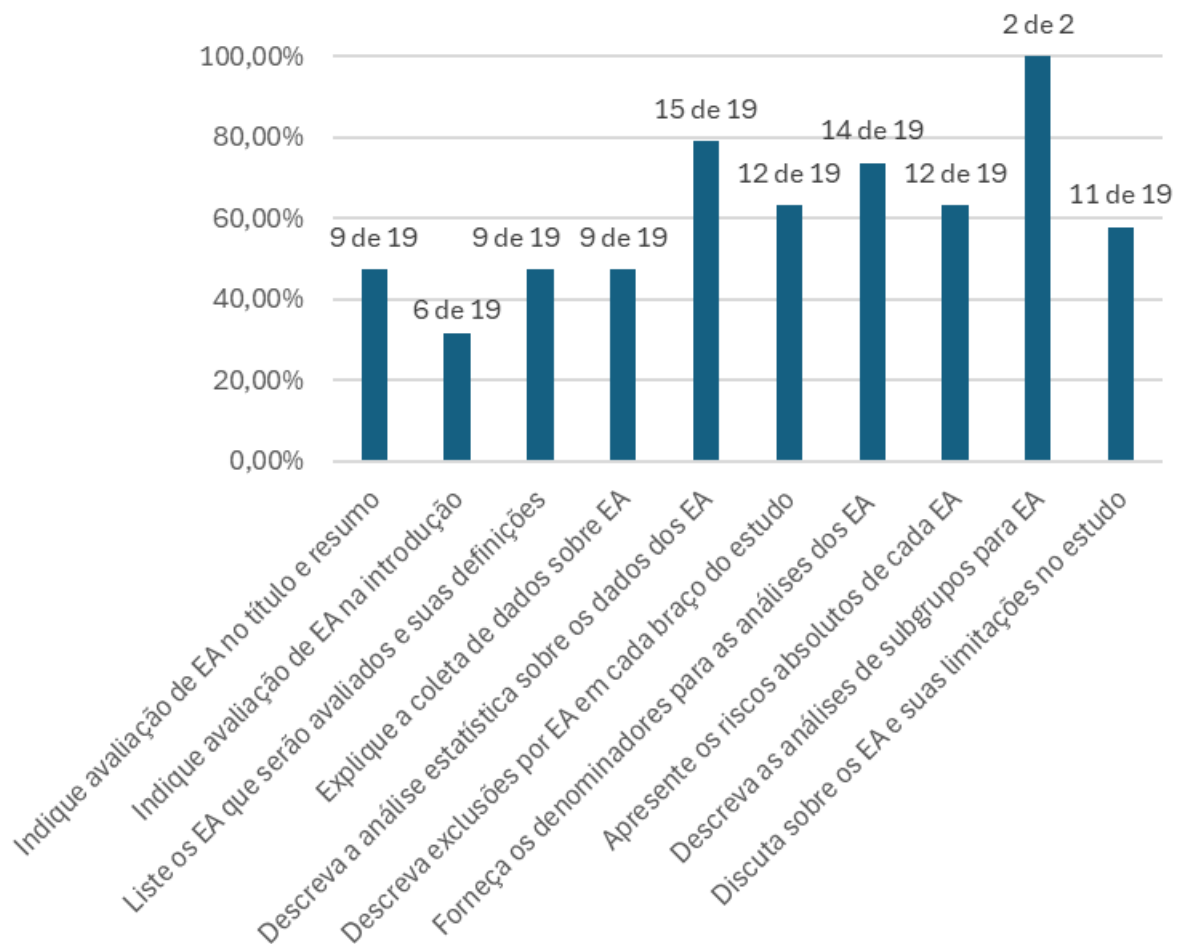
Dos sete estudos selecionados a partir de títulos e resumos, seis foram excluídos por diversas razões. Três teses de doutorado foram excluídas por ausência de grupo comparador para CQ ou HCQ (51-53). Um dos estudos não reportou eventos adversos (54). Uma das teses de doutorado foi excluída pois se tratava de outro desenho de estudo (55). Um estudo presente em anais de congresso foi excluído por falta de acesso ao texto na íntegra (56).

Quanto à avaliação da qualidade do relato dos eventos adversos, foram selecionados 19 estudos relacionados a COVID-19. Para cada um deles, foi avaliada a aderência às 10 recomendações da extensão do *Consolidated Standards Reporting Trials* (CONSORT), cujo resumo está descrito no APÊNDICE B.

A minoria dos estudos estava em conformidade com as recomendações dos primeiros quatro itens da extensão do CONSORT. Quarenta e sete por cento dos estudos seguiram a recomendação número 1, que se refere à citação da avaliação de eventos adversos nos títulos e resumos. Essa recomendação é importante para a apropriada indexação em banco de dados e para busca na literatura em estudos sobre segurança. Trinta e dois por cento dos estudos seguiram a recomendação 2 e 47% dos estudos seguiram as recomendações 3 e 4. As definições de cada recomendação estão apresentadas de forma detalhada no ANEXO A.

As recomendações com melhor aderência dos estudos avaliados foram as dos itens 5, 6, 7, 8 e 10. Tais recomendações foram cumpridas por 79%, 63%, 74%, 63% e 58% dos ECRs, respectivamente. As porcentagens de ECRs que atendem às recomendações individuais são mostradas na Figura 2.

Figura 2 – Porcentagem de aderência às recomendações da extensão do CONSORT de como reportar eventos adversos nos 19 ECR sobre COVID-19



Legendas: CONSORT=*Consolidated Standards of Reporting Trials*, ECR= Ensaio clínico randomizado, EA=eventos adversos

Fonte: elaborado pelo autor (2023)

A recomendação 9 da extensão do CONSORT se refere à avaliação da descrição de análise de subgrupo sobre eventos adversos. A maioria dos ECRs em COVID-19 dessa revisão não avaliaram a segurança como um desfecho primário. Dessa forma, a maior parte desses estudos também não apresentou análise de subgrupo relacionada a eventos adversos e, portanto, foram classificados nesse quesito com o termo “não se aplica” (NA). Apenas dois estudos apresentaram análise de subgrupo, ambos os quais relataram adequadamente esse aspecto.

Discussão

Considerando a possibilidade do uso de cloroquina (CQ) e hidroxiclороquina (HCQ) no tratamento da COVID-19 no início da pandemia, um número significativo de pacientes passou a fazer uso desses medicamentos, levando a preocupações quanto a sua segurança. Por isso, foi conduzida essa revisão sistemática de ensaios clínicos randomizados (ECR) para avaliar a segurança da CQ e HCQ em diferentes condições e populações.

Os desfechos primários foram a frequência de eventos adversos raros, mas potencialmente fatais, incluindo: eventos adversos graves (EAGs), retinopatia e complicações cardíacas. A avaliação de estudos publicados incluiu 106 ECRs, com um total de 24.879 participantes. Com certeza moderada, não houve evidência de que CQ e HCQ aumentaram a frequência de EAGs. No entanto, a HCQ aumentou a incidência de complicações cardíacas nos ECRs em COVID-19. Devido à imprecisão e ao risco de viés, não se observou efeito claro de CQ e HCQ sobre a retinopatia.

Embora a literatura tenha relatado diversos eventos adversos associados à CQ e HCQ, ambos os medicamentos são geralmente considerados seguros para outras condições (57-60). Uma possível explicação para o aumento das complicações cardíacas com o uso de HCQ na COVID-19 é que esses pacientes podem apresentar um maior risco de arritmias (61).

Em novembro de 2021, esses resultados foram publicados em meio à urgência da pandemia. Devido ao grande número de estudos incluídos na revisão, não foi possível, naquele momento, expandir as buscas por estudos não publicados e complementar a pesquisa com uma avaliação detalhada da qualidade do relato dos eventos adversos.

Revisões sistemáticas e meta-análises visam resumir as evidências da literatura de forma mais abrangente possível. A ausência de resultados de estudos que deveriam ter sido incluídos na síntese, pode levar a viés de publicação (62). A exclusão da literatura cinzenta, a qual inclui anais de congressos, relatórios de pesquisa, dados não publicados, dissertações e documentos oficiais, pode superestimar a eficácia de uma intervenção (63).

Em relação aos eventos adversos, a busca na literatura cinzenta parece ter ainda mais relevância. Há evidências de que o número e a variedade de eventos adversos são maiores em estudos não publicados, comparando-se com suas versões

publicadas (64, 65). Contudo, a maioria das revisões sistemáticas sobre eventos adversos exclui estudos não publicados (66).

Dessa forma, para reduzir o risco de viés de publicação, optou-se por incluir a busca por estudos não publicados nessa revisão. Apenas um estudo atendeu aos critérios de elegibilidade, no qual não houve relato de EAGs, retinopatia ou complicações cardíacas (50). No entanto, eventos adversos totais foram mais comumente observados nos grupos utilizando CQ e HCQ, dado semelhante ao encontrado nos estudos publicados da nossa revisão.

É importante ressaltar que os resultados desse estudo estavam disponíveis em formato de pré impressão, ou *preprint*, e que não foram publicados até o momento. *Preprints* são manuscritos divulgados na internet antes da revisão por pares e publicação em revistas, com o objetivo de facilitar o acesso e acelerar a disseminação de pesquisas científicas. No entanto, a divulgação pública sem revisão editorial pode levar a conclusões precipitadas e impactar negativamente a população. Portanto, os *preprints* devem idealmente passar por triagem antes da divulgação e não devem ser utilizados como guia para prática clínica (67).

Outro aspecto importante sobre os estudos que avaliam eventos adversos é a forma como esses são reportados. Um grande número de ECRs não fornecem os detalhes de definição e registro de tais eventos (68). Além disso, diferentes métodos de avaliação podem levar a diferentes incidências de eventos adversos nos resultados dos estudos (69). A fim de padronizar e melhorar a qualidade desses relatórios, foi desenvolvida a extensão da declaração *Consolidated Standards Reporting Trials* (CONSORT) (49).

De acordo com uma subanálise dos estudos sobre COVID-19 incluídos na nossa revisão, 40% das recomendações da extensão do CONSORT não foram adequadamente reportadas.

Embora o objetivo principal da maioria dos ECRs não seja a avaliação de eventos adversos, esses estudos oferecem uma compreensão inicial sobre a segurança de uma intervenção (70). Entretanto, a notificação de danos em ECRs costuma ser inadequada em diversas áreas médicas (71). Há evidências de que diferentes métodos de coleta e registro podem levar a resultados divergentes (72). Comparar as taxas de reações adversas entre ECRs que relatam danos de forma

diferente pode levar a resultados imprecisos. Essas circunstâncias representam um desafio no desenvolvimento de revisões sistemáticas sobre segurança (68).

Os resultados do nosso estudo podem ter sofrido uma influência por conta da adesão incompleta às recomendações da extensão do CONSORT. Uma revisão sistemática recente mostrou um aumento de mortalidade possivelmente relacionada a HCQ e CQ, contudo, trata-se de revisão de estudos observacionais (73). Nossa revisão não indicou que CQ e HCQ aumentam a frequência de EAGs, mesmo em análises de subgrupos por tipo de doença, como no caso da COVID-19.

Embora os ECRs sejam considerados o maior nível de evidência para estabelecer associações causais, deve-se considerar que esses estudos costumam proporcionar circunstâncias distintas das vivenciadas na prática clínica. Na maioria dos ECRs, são excluídos da avaliação: indivíduos muito idosos, pacientes com múltiplas comorbidades, participantes em uso concomitante de medicações com potencial de interação e com fatores de risco para eventos adversos. Dessa forma, uma limitação da nossa revisão é a inclusão exclusiva de ECRs, sendo a maioria deles não pragmáticos. Isso implica que o perfil de segurança de CQ e HCQ apresentado não foi projetado para o mundo real, o que poderia subestimar os danos.

Nesse contexto, a farmacovigilância representa uma importante estratégia para avaliação de eventos adversos, ao promover novos estudos após a aprovação dos medicamentos e ao estimular a notificação de eventos adversos observados na prática clínica.

Cloroquina (CQ) e hidroxiclороquina (HCQ) provavelmente não aumentam a frequência de eventos adversos graves (EAGs) em ensaios clínicos randomizados (ECRs) sobre COVID-19 e outras condições. No entanto, podem aumentar as complicações cardíacas em pacientes com COVID-19. Devido à imprecisão e ao risco de viés, não foi observado um efeito claro dessas medicações na incidência de retinopatia.

Apesar da importância do relato adequado de eventos adversos e da publicação das recomendações da extensão do CONSORT desde 2004, não houve adesão completa dos ECRs sobre COVID-19 a essas recomendações. Reforçamos a necessidade de reportar adequadamente os eventos adversos em ECRs para que haja uma avaliação mais precisa desses desfechos.

É importante observar que medicamentos como CQ e HCQ, que já possuem perfil de segurança conhecido para determinadas doenças, têm a possibilidade de levar a desfechos inesperados quando utilizados em outras condições. Diante disso, é essencial monitorizar criteriosamente possíveis eventos adversos de uma medicação, sempre que surgir uma nova indicação para a sua aplicação.

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ESTRATÉGIA DE BUSCA

20/04/2020 e 17/04/2021

PubMed

#1 "Hydroxychloroquine"[Mesh] OR (Oxychlorochin) OR (Oxychloroquine) OR (Hydroxychlorochin) OR (Plaquenil) OR (Hydroxychloroquine Sulfate) OR (Hydroxychloroquine Sulfate (1:1) Salt)

2"Chloroquine"[Mesh] OR (Chlorochin) OR (Chingamin) OR (Khingamin) OR (Nivaquine) OR (Chloroquine Sulfate) OR (Sulfate, Chloroquine) OR (Chloroquine Sulphate) OR (Sulphate, Chloroquine) OR (Aralen) OR (Arequin OR (Arequin) OR (Arechine)

#3 "chloroquine diphosphate" [Supplementary Concept] OR (chingamin phosphate) OR (unspecified phosphate of chloroquine diphosphate) OR (delagil) OR (khingamin phosphate) OR (arechin) OR (chloroquine phosphate) OR (Resochin) OR (chloroquine diphosphate, (+-)-isomer) OR (chloroquine diphosphate, (-)-isomer) OR (chloroquine bis(dihydrogenphosphate) dihydrate) OR (chloroquine diphosphate, (+)-isomer)

*4 randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh]))

*sensitivity- and precision-maximizing version (2008 revision); PubMed format – Cochrane

((("chloroquine diphosphate" [Supplementary Concept] OR (chingamin phosphate) OR (unspecified phosphate of chloroquine diphosphate) OR (delagil) OR (khingamin phosphate) OR (arechin) OR (chloroquine phosphate) OR (Resochin) OR (chloroquine diphosphate, (+-)-isomer) OR (chloroquine diphosphate, (-)-isomer) OR (chloroquine bis(dihydrogenphosphate) dihydrate) OR (chloroquine diphosphate, (+)-isomer)) OR ("Chloroquine"[Mesh] OR (Chlorochin) OR (Chingamin) OR (Khingamin) OR (Nivaquine) OR (Chloroquine Sulfate) OR (Sulfate, Chloroquine) OR (Chloroquine Sulphate) OR (Sulphate, Chloroquine) OR (Aralen) OR (Arequin OR (Arequin) OR (Arechine))) OR ("Hydroxychloroquine"[Mesh] OR (Oxychlorochin) OR (Oxychloroquine) OR (Hydroxychlorochin) OR (Plaquenil) OR (Hydroxychloroquine Sulfate) OR (Hydroxychloroquine Sulfate (1:1) Salt))) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh]))))

Total= 1543

EMBASE

'hydroxychloroquine'/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' OR 'chloroquinol' OR 'ercoquin' OR 'hydrochloroquine' OR 'hydrocloroquine' OR 'oxychloroquine' OR 'quensyl' OR 'sn 8137'

'hydroxychloroquine sulfate'/exp OR '1 (7 chloro 4 quinolylamino) 3 diethylamino 2 propanol sulfate' OR '1 (7 chloro 4 quinolylamino) 3 diethylamino 2 propanol sulphate' OR '2 [[4 [(7 chloro 4 quinoliny) amino] pentyl] (ethyl) amino] ethanol sulfate' OR '2 [[4 [(7 chloro 4 quinoliny) amino] pentyl] (ethyl) amino] ethanol sulphate' OR '2 [[4 [(7 chloroquinolin 4 yl) amino] pentyl] (ethyl) amino] ethanol sulfate' OR '2 [[4 [(7 chloroquinolin 4 yl) amino] pentyl] (ethyl) amino] ethanol sulphate' OR '7 chloro 4 (3 diethylamino 2 hydroxypropylamino) quinoline sulfate' OR '7 chloro 4 (3 diethylamino 2 hydroxypropylamino) quinoline sulphate' OR 'dimard' OR 'erquin' OR 'evoquin' OR 'geniquin' OR 'hydroxychloroquine sulphate' OR 'oxiklorin' OR 'oxychloroquine sulfate' OR 'oxychloroquine sulphate' OR 'plaquenil' OR 'plaquenil sulfate' OR 'plaquenil sulphate' OR 'plaquinol' OR 'toremonil' OR 'yuma'

'chloroquine'/exp OR '4 (4 diethylamino 1 methylbutylamino) 7 chlorochinolin diphosphate' OR '4 (4 diethylamino 1 methylbutylamino) 7 chlorochinolin sulfate' OR '4 (4 diethylamino 1 methylbutylamino) 7 chlorochinolin sulphate' 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 'avlocor' OR 'avoclor' OR 'bemaphata' OR 'bemaphate' OR 'bemasulph' OR 'bipiquin' OR 'cadiquin' OR 'chemochin' OR 'chemochine' OR 'chingamine' OR 'chingaminum' OR 'chloraquine' OR 'chlorochi' 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 'klorokinofosfat' 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 'resochoen' OR 'resochoene' OR 'resochoin' OR 'resochoin junior' OR 'resochina' OR 'resochine' OR 'resochoinon' 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 '7618' OR 'w7618' OR 'win 244' OR 'win244'

Filter

best optimization of sensitivity and specificity*

random*:ab,ti OR placebo*:de,ab,ti OR (double NEXT/1 blind*):ab,ti

*Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association: JMLA. 2006 Jan;94(1):41-7

Total=3726

CENTRAL

Search Name:

Date Run: 20/04/2020 10:37:49

Comment:

ID	Search	Hits
#1	MeSH descriptor: [Hydroxychloroquine] explode all trees	302
#2	'Hydroxychloroquine Sulfate Salt' OR 'Hydroxychloroquine Sulfate' OR 'Plaquenil' OR 'Hydroxychlorochin' OR 'Oxychlorochin' OR 'Oxychloroquine'	104
#3	MeSH descriptor: [Chloroquine] explode all trees	976
#4	'Chloroquine Sulphate' OR 'Chloroquine Sulfate' OR 'Sulphate, Chloroquine' OR 'Sulfate, Chloroquine'	35
#5	#1 OR #2 OR #3 OR #4	1055

BVS (Lilacs, IBECs, Hanseniase, Sec Muni SP, Coleciona Sus)

#1 MH:"Hidroxicloroquina" OR (Oxicloroquina) OR MH: D03.633.100.810.050.180.350\$

#2 MH:"Cloroquina" OR MH: D03.633.100.810.050.180\$

#1 OR #2= 156

Trip Database

Hydroxychloroquine, filter controlled trial 199

Chloroquine, filter controlled trial 549

SCOPUS

LL (" Hydroxychloroquine") OR ALL (" Chloroquine ") AND ALL ("randomized
controlled trial") AND NOT INDEX (medline) AND (LIMIT-
TO (DOCTYPE , "ar"))

Total= 866

APÊNDICE A – Modelo de extração para avaliação da qualidade do relato dos eventos adversos com base nas recomendações da extensão do CONSORT

	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10
ECR1	sim	não	não	sim	não	sim	não	sim	sim	sim
ECR 2	sim	sim	sim	não	sim	não	sim	não	não	não
ECR 3	sim	sim	sim	sim	não	não	não	sim	não	sim

Legenda: ECR=Ensaio Clínico Randomizado

Fonte: elaborado pelo autor (2023)

APÊNDICE B – Avaliação da qualidade do relato dos eventos adversos reportados
com base nas recomendações da extensão do CONSORT

Estudos	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10
Abella	sim	não	não	sim	sim	sim	sim	sim	NA	sim
Barnabas	sim	não	não	não	sim	sim	sim	não	NA	não
Boulware	sim	não	não	não	sim	sim	sim	não	NA	não
Cavalcanti	não	não	não	não	sim	não	sim	sim	NA	sim
Chen Jun	não	sim	não	não	sim	sim	não	não	NA	não
Chen Zhaowei	não	não	não	não	não	não	sim	não	NA	não
Cheng-Pin-Chen	não	sim	sim	não	sim	sim	não	sim	NA	sim
Dubee	não	sim	sim	não	sim	sim	sim	sim	NA	sim
Johnston	não	não	sim	não	sim	sim	não	não	NA	sim
Lyngbakken	não	sim	sim	sim	sim	não	não	não	NA	sim
Mitjá	sim	sim	sim	sim	sim	sim	sim	sim	NA	sim
Omrani	sim	não	não	sim	sim	sim	sim	sim	NA	sim
Rajasingham	não	não	não	sim	não	não	sim	sim	sim	não
Recovery	não	não	não	não	não	não	sim	sim	NA	sim
Reis	sim	não	sim	sim	sim	sim	não	não	NA	não
Self	não	não	sim	sim	sim	sim	sim	sim	NA	não
Skipper	sim	não	não	sim	não	não	sim	sim	NA	não
Tang	sim	sim	sim	Não	sim	sim	sim	sim	NA	sim
Ulrich	sim	não	sim	sim	sim	não	sim	sim	sim	sim

Legenda: CONSORT = *Consolidated Standards of Reporting Trials*; NA = não se aplica

Fonte: elaborado pelo autor (2023)

ANEXO A – As 10 recomendações de efeitos adversos do CONSORT

Recomendação	Descrição
1	Caso o estudo tenha coletado dados sobre eventos adversos e benefícios, isso deve estar indicado no título e no resumo
2	Caso o ensaio clínico aborde eventos adversos, bem como benefícios, isso deve estar indicado na introdução
3	Lista dos eventos adversos com definições para cada um (atenção, relevância, classificação, eventos esperados versus inesperados, referência a definições padronizadas e validadas e descrição de novas definições)
4	Esclarecer como as informações relacionadas aos eventos adversos foram coletadas (modo de coleta de dados, tempo, métodos de atribuição, intensidade de apuração e regras de monitoramento e interrupção relacionadas aos eventos adversos, se pertinente)
5	Descrever planos para apresentar e analisar informações sobre efeitos adversos (incluindo codificação, manejo de eventos recorrentes, especificação de problemas com tempo, manejo de medidas contínuas e qualquer análise estatística)
6	Descrever, para cada braço do estudo, a exclusão de participantes causadas por danos e a experiência com o tratamento alocado em cada grupo
7	Providenciar os denominadores para as análises dos eventos adversos
8	Apresentar os riscos absolutos de cada evento adverso (especificando tempo, grau e seriedade para cada braço do estudo) e apresentar métricas apropriadas para evento recorrente, variáveis contínuas e variáveis de escala, sempre que pertinente
9	Descrever quaisquer análises de subgrupos e análises exploratórias sobre eventos adversos
10	Proporcionar uma discussão equilibrada dos benefícios e malefícios, com ênfase nas limitações do estudo, generalização e outras fontes de informação sobre os eventos adversos

Fonte: Ioannidis (2004)

ANEXO B – Questões centrais do ICEMAN para versão de meta-análises

1	A análise da modificação do efeito é baseada na comparação dentro e não entre os ensaios?
2	Para comparações dentro dos grupos, os efeitos de modificação foram similares entre os estudos?
3	Para comparações entre grupos, o número de estudos é grande?
4	A direção do efeito modificador foi corretamente apresentada em hipótese a priori?
5	O teste de interação sugere que há uma chance de uma explicação improvável do aparente efeito modificador?
6	Os autores testaram apenas um pequeno número de efeitos modificadores ou consideraram o número de efeitos modificadores na análise estatística?
7	Os autores adotaram modelos de efeitos aleatórios?
8	Se o efeito modificador é uma variável contínua, um ponto de corte arbitrário foi evitado?

Legendas: ICEMAN = Instrument to assess the Credibility of Effect Modification Analyses

Fonte: Schandelmaier (2020)

Registro do protocolo da revisão na PROSPERO

Systematic review

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Systematic review of safety of chloroquine and hydroxychloroquine from malarial and non-malarial randomized controlled trials – a prospection for COVID-19 management

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

27/03/2020

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

30/06/2020

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: Yes

Review stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Vania dos Santos Nunes-Nogueira

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Professor Nunes-Nogueira

7. * Named contact email.

Give the electronic mail address of the named contact.

vania.nunes-nogueira@unesp.br

8. Named contact address

Give the full postal address for the named contact.

Faculdade de Medicina - Câmpus de Botucatu

Av. Prof. Mário Rubens Guimarães Montenegro, s/n - UNESP - Campus de Botucatu - Botucatu/SP - CEP 18618687

Pabx: (14) 3880-1001

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

551438801171

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

São Paulo State University-Medical School

Organisation web address:

<https://www.fmb.unesp.br/>

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country are now mandatory fields for each person.**

Dr Vania dos Santos Nunes-Nogueira. São Paulo State University - Medical School, UNESP, Botucatu, Sao Paulo, Brazil

Mayra Souza Botelho. São Paulo State University, Medical School, Botucatu, Sao Paulo, Brazil

Lehana Thabane. Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

São Paulo State University, Medical School, UNESP, Botucatu, Sao Paulo, Brazil

Grant number(s)

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country are now mandatory fields for each person.**

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

From randomized controlled trials are chloroquine and hydroxychloroquine safe for malarial and non-malarial conditions?

16. * Searches.

State the sources that will be searched. Give the search dates, and any restrictions (e.g. language or publication period). Do NOT enter the full search strategy (it may be provided as a link or attachment.)

Four general research strategies will be applied to the main electronic health databases: Embase (Elsevier, 1980-2020), MEDLINE (PubMed, 1966-2020), and LILACS (Virtual Health Library, 1982-2020) of Controlled Clinical Trials of the Cochrane Collaboration (CENTRAL - Cochrane). The search strategies will contain index terms and synonyms of chloroquine, hydroxychloroquine. PubMed will use the filter for randomized

studies, as supported by Cochrane and the embedded filter will be used for the same purpose in Embase.

There will be no language or year restrictions

17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy. Do NOT provide links to your search results.

#1 "Hydroxychloroquine"[Mesh] OR (Oxychlorochin) OR (Oxychloroquine) OR (Hydroxychlorochin) OR (Hydroxychloroquin) OR (Hydroxychloroquine) OR (Chloroquine Sulfate) OR (Chloroquine Sulphate) OR (Chloroquine Sulfate) OR (Sulfate, Chloroquine) OR (Chloroquine Sulphate) OR (Sulphate, Chloroquine) OR (Aralen) OR (Arequin OR (Arequin) OR (Arechine)

#3 "chloroquine diphosphate" [Supplementary Concept] OR (chingamin phosphate) OR (unspecified phosphate of chloroquine diphosphate) OR (delagil) OR (khingamin phosphate) OR (arechin) OR (chloroquine phosphate) OR (Resochin) OR (chloroquine diphosphate, (+)-isomer) OR (chloroquine diphosphate, (-)-isomer) OR (chloroquine bis(dihydrogenphosphate) dihydrate) OR (chloroquine diphosphate, (+)-isomer)

#4 *(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh]))

*sensitivity- and precision-maximizing version (2008 revision); PubMed format; Cochrane Filter

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Chloroquine and hydroxychloroquine were originally developed for the treatment of malaria; however, many additional drug properties were discovered, and they have been successfully used to treat several non-malarial conditions as rheumatological, dermatology and immunological conditions. And there is a growing body of evidence to support their therapeutic potential in oncology, chronic kidney disease, HIV infection and other viral infections. Faced with the health crisis installed with the COVID-19 pandemic, and the absence of a specific drug therapy until then, chloroquine and hydroxychloroquine are being evaluated for their possible effectiveness in the treatment of this disease. Since then, several clinical trials have been conducted in order to evaluate the efficacy and safety of chloroquine and hydroxychloroquine in the treatment of patients affected by the infection with the new Coronavirus

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Individuals, regardless of gender and age, diagnosed with a malarial or non-malarial condition, whose treatment was with either chloroquine or hydroxychloroquine.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

We will consider as intervention either chloroquine or hydroxychloroquine.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

The comparison group will be no chloroquine or no hydroxychloroquine (placebo or no comparison for the intervention).

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

We will select randomized controlled trials.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

The primary outcomes will be the number of patients with serious adverse effect (SAE), the number of patients with retinopathy and the number of patients with cardiac complications.

*** Measures of effect**

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

The relative risk will be calculated with 95% confidence intervals (CIs) as the estimate of the intervention effect.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

The secondary outcomes will be the total number of participants with any chloroquine or hydroxychloroquine related adverse effects, the number of withdrawals due to chloroquine or hydroxychloroquine related adverse effects, the number of patients with gastrointestinal adverse effects, the number of patients with cutaneous manifestations, the number of patients with myopathy, number of patients with visual symptoms, number of patients with auditory symptoms.

* Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

The relative risk will be calculated with 95% confidence intervals (CIs) as the estimate of the intervention effect.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Two reviewers will use a standard form to extract the following data from the selected studies: year of publication, country, basal disorder, population group (children, adults, 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, mean age of participants.

27. * Risk of bias (quality) assessment.

Describe the method of assessing risk of bias or quality assessment. State which characteristics of the studies will be assessed and any formal risk of bias tools that will be used.

For each selected trial, the risk of bias will be assessed according to the criteria described in the revised Cochrane risk-of-bias tool for randomized trials (RoB 2 tool), which considers for each outcome evaluated five domains: (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 will be evaluated in pairs and independently by ten reviewers as having low risk of bias, some concerns, and high risk of bias. In case of disagreement, there will be a discussion between the reviewers before the final classification.

28. * Strategy for data synthesis.

Provide details of the planned synthesis including a rationale for the methods selected. This **must not be generic text** but should be **specific to your review** and describe how the proposed analysis will be applied to your data.

Similar outcomes in at least two studies will be plotted in the meta-analysis using the Stata Statistical Software 12 (Stata Statistical Software: Release 12. College Station, TX: StataCorp LLC). A random-effects model will be used for the meta-analysis. If quantitative synthesis is not appropriate, a narrative synthesis will

be provided.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

If enough data are available, subgroup analyses will be performed according to patient diagnosis, type of population (children, adult, pregnant women), type of intervention (CQ or HCQ), daily dosage (less than 500 mg versus higher than 500 mg for CQ, less than 400 mg versus higher than 400 mg for HCQ), time of follow up (up to four weeks versus after four weeks).

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness

No

Diagnostic

No

Epidemiologic

No

Individual patient data (IPD) meta-analysis

No

Intervention

Yes

Meta-analysis

No

Methodology

No

Narrative synthesis

No

Network meta-analysis

No

Pre-clinical

No

Prevention

No

Prognostic

No

Prospective meta-analysis (PMA)

No

Review of reviews

No

Service delivery

No

Synthesis of qualitative studies

No

Systematic review

Yes

Other

No

Health area of the review

Alcohol/substance misuse/abuse

No

Blood and immune system

No

Cancer

No

Cardiovascular

No

Care of the elderly

No

Child health

No

Complementary therapies

No

Crime and justice

No

Dental

No

Digestive system

No

Ear, nose and throat

No

Education

No

Endocrine and metabolic disorders

No

Eye disorders

No

General interest

No

Genetics

No

Health inequalities/health equity

No

Infections and infestations

Yes

International development

No

Mental health and behavioural conditions

No

Musculoskeletal

No

Neurological

No

Nursing

No

Obstetrics and gynaecology

No

Oral health

No

Palliative care

No

Perioperative care

No

Physiotherapy

No

Pregnancy and childbirth

No

Public health (including social determinants of health)

No

Rehabilitation

No

Respiratory disorders

No

Service delivery

No

Skin disorders

No

Social care

No

Surgery

No

Tropical Medicine

No

Urological

No

Wounds, injuries and accidents

No

Violence and abuse

No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Brazil

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with

The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published. For newregistrations the review must be Ongoing.

Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

Give the link to the published review.

Outro artigo publicado durante o doutorado



Treatment of non-functioning pituitary adenoma with cabergoline: a systematic review and meta-analysis

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Abstract

Purpose To make a systematic review and meta-analysis of studies evaluating the effect of cabergoline (CBG) in the treatment of non-functioning pituitary adenomas (NFPAs).

Methods The primary outcome was tumor shrinkage, using as cut-off a reduction of at least 20% of the NFPA size from baseline. The secondary outcomes were prevention of tumor progression, clinically required additional interventions and adverse events (AE). Search strategies were applied to MEDLINE, EMBASE, LILACS and CENTRAL. Independent reviewers assessed the study eligibility, extracted data, and evaluated risk of bias. Random meta-analysis for the proportion of tumor shrinkage, prevention of tumor progression, clinically required additional interventions and frequency of AE were conducted.

Results Five studies were included. The meta-analysis of proportion was 19% for tumor shrinkage (95% CI 8–38%, 4 studies, 108 participants), 50% for prevention of tumor progression (95% CI 35–64%, 5 studies, 187 participants), 14% for clinically required additional interventions (95% CI 6–30%, 4 studies, 128 participants) and 2% for adverse events (95% CI 1–6%, 3 studies, 157 participants).

Conclusions Effect of CBG to promote tumor shrinkage in NFPAs was low, while prevention of tumor progression after surgery was seen in half of the cases, with a low frequency of adverse events.

Systematic review registration PROSPERO CRD42020206778.

Keywords Cabergoline · Dopamine agonists · Pituitary neoplasms · Non-functioning pituitary adenoma · Systematic review

Introduction

Non-functioning pituitary adenomas (NFPAs) are benign tumors of the sellar region and are diagnosed by the absence of clinical and biochemical evidence of hormone hypersecretion. These lesions may be asymptomatic or lead to hypothalamic/pituitary dysfunction or mass effect symptoms,

such as visual loss and headache, due to their large size at diagnosis [1, 2]. NFPAs account for one-third of all pituitary tumors and are among the most common type of macroadenomas [2].

Transsphenoidal pituitary surgery is the treatment of choice for NFPAs in symptomatic patients or in cases where there are signs of imminent visual loss. However, the difficulty of complete resection of large or invasive tumors and recurrence are frequent problems in the management of these tumors [3, 4]. Radiotherapy (RT) is an alternative treatment that shows high rates of tumor control, but it is also associated with an increased risk of complications, especially hypopituitarism, and mortality [4, 5].

Management of functioning pituitary adenomas with medical therapy is commonly performed, but it is not well-established for NFPAs [6]. Based on the findings that NFPAs express dopaminergic receptors (DRs), such as D2, dopamine agonists (DAs) have been used as an option for preventing tumor recurrence or regrowth after surgery [6, 7].

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Comentário a ser submetido

Commentary on “Systematic review and metaanalysis of the safety of chloroquine and hydroxychloroquine from randomized controlled trials on malarial and non-malarial conditions”

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Abstract

The use of chloroquine (CQ) and hydroxychloroquine (HCQ) in the COVID-19 pandemic raised concerns about their adverse events (AE). Therefore we performed a systematic review to evaluate the safety of CQ and HCQ in malaria and other condition(74). In this commentary, we added a search of the gray literature and an assessment of the quality of reporting AEs to the review

The absence of unpublished studies in systematic reviews and meta-analyses can lead to publication bias, hence it is desirable to add gray literature to the search. For this reason we performed a search in the gray literature from November 2004 until April 2021. Only one study met the eligibility criteria, in which there were no serious adverse events (SAE).

We also performed a subanalysis of the COVID-19 studies included in the review, using the extension to the CONSORT (Consolidated Standards of Reporting Trials) statement on how to report AEs. Among the 10 recommendations of the CONSORT extension, 40% of them were not adequately reported in the COVID-19 studies.

Despite the importance of adequate reporting of AEs in RCTs, with the CONSORT extension published since 2004, it appears that there is no strict adherence to these recommendations in recent studies. We reinforce the need to adequately report AEs for a more accurate assessment of these outcomes.

Keywords: Chloroquine, Hydroxychloroquine, COVID-19, Adverse effects, Safety, Systematic review, Gray Literature

Textbox with key messages

- Our systematic review showed that CQ and HCQ do not increase SAE, but may increase cardiac complications, especially in COVID-19.
- In this commentary, we added a search of the gray literature and an assessment of the quality of reporting AEs.
- There is a lack of evidence supporting the use of CQ and HCQ in treating COVID-19 from the randomized controlled trials (RCT) included in this review.
- Improved reporting of AEs in RCTs is required by adhering to the CONSORT extension on how to report AEs.

Background

In view of the COVID-19 pandemic and the absence of specific therapy so far, chloroquine (CQ) and hydroxychloroquine (HCQ) were used to treat this condition in most countries, despite the lack of clear evidence of their efficacy. This raised concerns about adverse events (AE) related to these drugs. In this context, we performed a systematic review to evaluate the safety of CQ and HCQ in malaria and other conditions(74).

In this commentary, we added to the review a search of the gray literature and an assessment of the quality of reporting adverse events (AEs) based on the 10 recommendations of the CONSORT (Consolidated Standards of Reporting Trials) extension on how to report AEs (49).

Main text

Systematic reviews and metaanalyses aim to summarize evidence of the literature in a broad and unbiased way. The absence of results from studies that should have been included in the synthesis can lead to publication bias (62). Excluding gray literature, which comprises reports, dissertations, theses and conference abstracts, may overestimate the effectiveness of an intervention (63). To reduce the risk of publication bias, it is desirable to add gray literature to the search in addition to published studies (62).

In November 2021, we published the article "Systematic review and metaanalysis of the safety of chloroquine and hydroxychloroquine from randomized controlled trials on malarial and non-malarial conditions" due to concerns about the AEs of these drugs in COVID-19(74). Our results showed that CQ and HCQ probably do not increase serious adverse events (SAE), but there was a possible increase in cardiac complications, especially in patients with COVID-19. However, given the context of the pandemic, there was not enough time to expand our searches to gray literature.

Regarding AEs, the search for gray literature seems to be even more relevant. There is evidence that the number and range of AEs are higher in unpublished studies compared to their published versions on the same issue (64, 65). Nevertheless, most systematic reviews on AEs still do not include unpublished studies(66).

After publication, we were able to perform a search on Google scholar, Web of Science, Web of Knowledge Conference Proceedings Citation Indexes, theses and dissertations (Brazilian Digital Library of Theses and Dissertations, CAPES Theses and Dissertations Catalog, Digital Library of Theses and Dissertations from USP and in the UNESP Institutional Repository) and regulatory agency websites (ANVISA, FDA and EMA) from November 2004 (when the CONSORT extension for reporting AEs was published) until April 2021. Only one study met the eligibility criteria, in which there were no SAE, although total AEs were more commonly observed in the CQ and HCQ groups (50).

Another important aspect about studies that evaluate AEs is how these events have been reported. A large number of randomized controlled trials (RCT) have failed to provide details on how AEs were defined and recorded (68). Furthermore, different methods of assessing AEs can lead to different incidences of these events in study results (69). Therefore, an extension to the CONSORT statement was developed in order to standardize and improve the quality of these reports (49).

Also after publication, we performed a subanalysis of the COVID-19 studies included in the review, using the extension to the CONSORT statement on how to report AEs. Among the 10 recommendations of the CONSORT extension, 40% of them were not adequately reported in the COVID-19 studies. In table 1, we provide a summary of the CONSORT extension recommendations.

The minority of studies (47%) indicated in the title or abstract that harm or AEs would be assessed. Adherence to this recommendation is important for database indexing

and information retrieval. Only 32% of the studies considered the assessment of AEs as one of the objectives in the introduction. Furthermore, only 47% of the studies listed in detail all the AEs that would be evaluated with their appropriate definitions and the methods for collecting this data. The percentage of RCTs complying with individual recommendations is shown in figure 1.

Recommendation 9 of the CONSORT extension refers to the evaluation of the description of subgroup analyzes on AEs. Only two studies had a subgroup analysis involving AEs, both of which adequately reported this aspect. For that reason the percentage of 100% is indicated for recommendation 9 in figure 1.

Although the main objective of most randomized controlled trials (RCTs) might not be safety assessment, they play a significant role in offering initial insights into the safety of a potential intervention(70). Meanwhile, the reporting of harms in RCTs across various medical fields has been identified as inadequate(71). Regarding AE data collection methods, for example, there is evidence that different methods of recording AEs can lead to significantly different results(72). Inconsistent reporting of AEs has significant consequences. Comparing AE rates between RCTs that report harm differently can lead to inaccurate results. These circumstances pose a challenge in the development of systematic reviews on this subject (68).

Poor adherence to CONSORT extension recommendations in the reporting of AE in the COVID-19 RCTs included in our study may have had an impact on our results. Our review did not indicate that CQ/HCQ increased the frequency of SAE, even in subgroup analysis by disease type, as in COVID-19. However, a recent systematic review and a meta-analysis of cohort studies showed a high number of probably HCQ-related deaths(73).

Conclusions

Despite the importance of adequate reporting of AEs in RCTs, with the CONSORT extension published since 2004, it appears that there is no strict adherence to these recommendations in recent studies. We reinforce the need to adequately report AEs for a more accurate assessment of these outcomes. It is also important to note that medications that already have a known safety profile for certain diseases, such as CQ and HCQ, can lead to unexpected consequences in other conditions. Therefore, it is essential to conduct a careful assessment of harms each time a new indication for a particular medication appears.

List of abbreviations

AE: Adverse event; ANVISA: Agência Nacional de Vigilância Sanitária; CAPES: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; CONSORT: Consolidated Standards of Reporting Trials; CQ: Chloroquine; EMA: European Medicines Agency; FDA: Food and Drug Administration; HCQ: Hydroxychloroquine; RCT: Randomized controlled trial; SAE: Serious adverse events; UNESP: Universidade Estadual Paulista "Júlio de Mesquita Filho"; USP: Universidade de São Paulo.

Competing interests

The authors have no conflicts of interest to declare.

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Authors' contributions

VSNN and LT conceptualized and designed the study. VSNN developed the search strategies. VSNN and MSB independently screened eligible studies and extracted data from included studies. VSNN and MSB performed the analysis of the studies, using the extension to the CONSORT statement on how to report AEs. VSNN supervised all the phases of this study and refereed any disagreement to avoid errors. All authors critically revised the manuscript and approved its final version.

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Figures, tables and additional files

Fig1. Percentage compliance with individual recommendations of the 2004 CONSORT extension for better harms reporting by 19 RCT on COVID-19

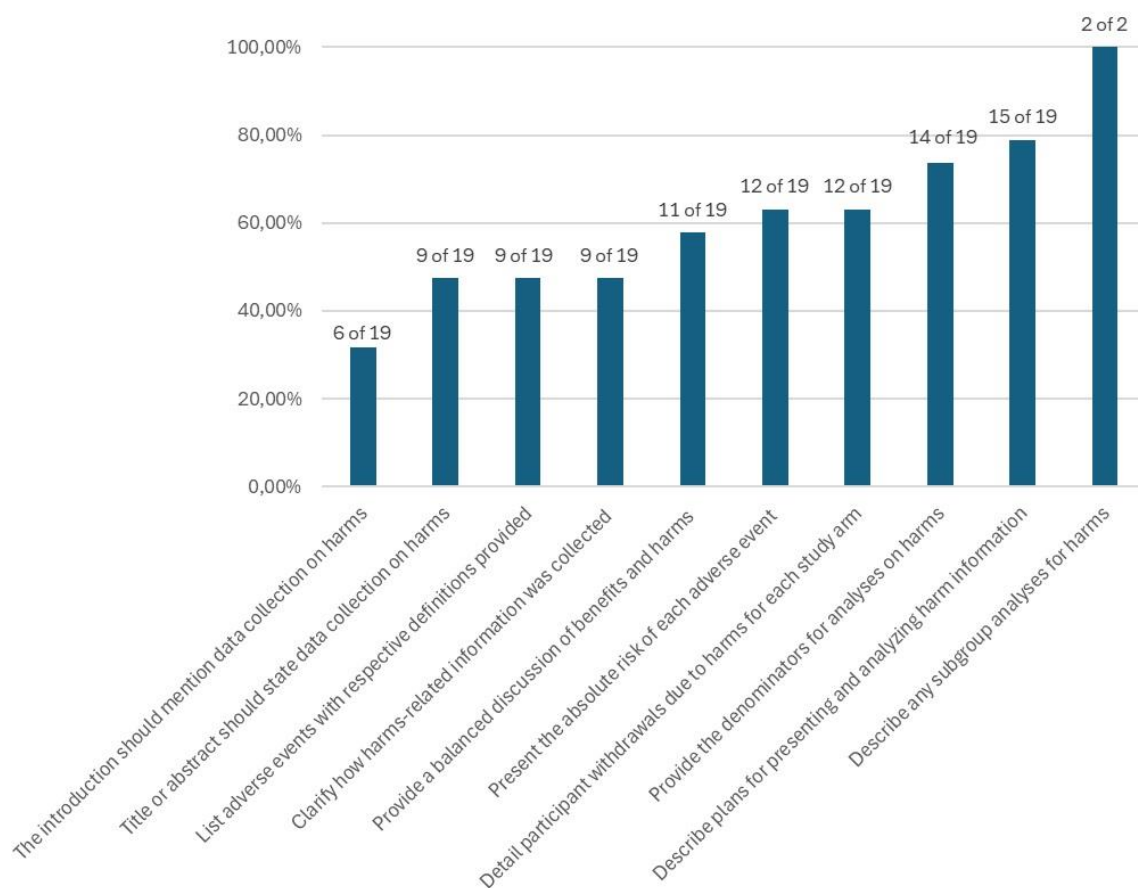


Table 1.

Summary of the 2004 CONSORT extension Better Reporting of Harms in Randomized Trials

Number	Recommendation
1	If study collected data on harms and benefits, the title or abstract should so state
2	If the trial addresses both harms and benefits, the introduction should so state.
3	List addressed adverse events with definitions for each (with attention, when relevant, to grading, expected vs. unexpected events, reference to standardized and validated definitions, and description of new definitions)
4	Clarify how harms-related information was collected (mode of data collection, timing, attribution methods, intensity of ascertainment, and harms-related monitoring and stopping rules, if pertinent)
5	Describe plans for presenting and analysing information on harms (including coding, handling of recurrent events, specification of timing issues, handling of continuous measures, and any statistical analyses)
6	Describe for each arm, the participant withdrawals that are because of harms and the experience with the allocated treatment
7	Provide the denominators for analyses on harms
8	Present the absolute risk of each adverse event (specifying type, grade and seriousness per arm), and present appropriate metrics for recurrent events, continuous variables and scale variables, whenever pertinent
9	Describe any subgroup analyses and exploratory analyses for harms
10	Provide a balanced discussion of benefits and harms with emphasis on study limitations, generalisability, and other sources of information on harms