REVIEW ARTICLE
ARTIGO DE REVISÃO

Enough with the madness: a systematic review and meta-analysis of hydroxychloroquine for COVID-19

Chega de loucura: uma revisão sistemática e metanálise de hidroxicloroquina para COVID-19

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Keywords:
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ABSTRACT

Objective: Because of preliminary results from *in vitro* studies, hydroxychloroquine (HCQ) and chloroquine (CQ) have been proposed as possible treatments for COVID-19, but the clinical evidence is discordant. This study aims to evaluate the safety and efficacy of CQ and HCQ for the treatment of COVID-19. **Methods:** A systematic review with meta-analysis was performed. An electronic search was conducted in four databases for randomized controlled trials that compared HCQ or CQ with standard-of-care. A complementary search was performed. A quantitative synthesis of clinical outcomes was performed using the inverse variance method adjusting for a random-effects model. **Results:** In total, 16 studies were included. The meta-analysis found no significant difference between intervention and control groups in terms of mortality at the most extended follow-up (RR = 1.09, CI95% = 0.99-1.19, p-value = 0.08), patients with negative PCR results (RR = 0.99, CI95% = 0.89-1.10, p-value = 0.86), or serious adverse events (RR = 2.21, CI95% = 0.89-5.47, p-value = 0.09). HCQ was associated with an increased risk of adverse events (RR = 2.28, CI95% = 1.36-2.83, p-value < 0.01). The quality of evidence varied from very low to high. **Conclusion:** There is no evidence that HCQ reduces the risk of death or improves cure rates in patients with COVID-19, but it might be associated with an increased risk of adverse events.

Palavras-chave:
COVID-19, cloroquina, hidroxicloroquina, revisão

RESUMO

Objetivo: Devido aos resultados preliminares de estudos *in vitro*, a hidroxicloroquina (HCQ) e a cloroquina (CQ) foram propostas como possíveis tratamentos para a COVID-19, mas as evidências clínicas são discordantes. Este estudo tem como objetivo avaliar a segurança e a eficácia da CQ e

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HCQ no tratamento da COVID-19. **Métodos:** Foi realizada uma revisão sistemática com metanálise. Uma busca eletrônica foi realizada em quatro bancos de dados por ensaios clínicos randomizados que compararam a HCQ ou CQ com o tratamento-padrão. Uma busca complementar foi realizada. Uma síntese quantitativa dos resultados foi realizada usando o método de variância inversa para um modelo de efeitos aleatórios. **Resultados:** No total, 16 estudos foram incluídos. A metanálise não encontrou nenhuma diferença significativa entre os grupos de intervenção e controle em termos de mortalidade no acompanhamento mais longo (RR = 1,09, IC95% = 0,99-1,19, valor-p = 0,08), pacientes com resultados de PCR negativos (RR = 0,99, IC95% = 0,89-1,10, valor-p = 0,86) ou eventos adversos graves (RR = 2,21, IC95% = 0,89-5,47, valor-p = 0,09). HCQ foi associada a um risco aumentado de eventos adversos (RR = 2,28, IC95% = 1,36-2,83, valor-p < 0,01). A qualidade da evidência variou de muito baixa a alta. **Conclusão:** Não há evidências de que a HCQ reduza o risco de morte ou aumente a taxa de cura em pacientes com COVID-19, mas pode estar associada a um risco aumentado de eventos adversos.

Introduction

COVID-19 has become a severe respiratory pandemic since its inception in 2019 (Ahn *et al.*, 2020; Heymann & Shindo, 2020). The high transmission rates and lethality (around 3%) (Roser *et al.*, 2020; Worldometer, 2021) provoked an intense social distancing policy and a decrease in socioeconomic activities to avoid the collapse of health systems and the loss of human lives. On March 30th, 2021, 128 million cases were reported worldwide, with over 2.8 million deaths. The overall incidence and mortality were 16,486 and 360.3 cases per million people in the world. Brazil, specifically, was heavily hit by the disease, with 12,577,354 cases and 314,268 deaths until March 30th, 2021. These numbers represent a cumulative incidence and mortality of 58,861 and 1,471 per million individuals (Worldometer, 2021). These data, however, may have been underestimated due to lack of testing or under-reporting in some places. Brazil, specifically, only tested symptomatic individuals. The behavior of the Brazilian president and the federal government has not helped the situation (Teixeira *et al.*, 2020; Fonseca *et al.*, 2021). On many occasions, the president undermined the seriousness of the pandemics, the importance of the vaccination programs and even made graceless jokes about its application in the population (BBC News, 2020; AFP, 2021; G1, 2021b; Gielow, 2021). He discouraged masks and mocked the social distancing measures (Andrade, 2020; Krüger, 2021). Because of the president and his Ministers of Health's divergence associated with social pressure, Brazil has already had four Ministries of Health during the pandemic (Biernath & Alvim, 2021).

Despite lacking knowledge on the matter, the president and some of his supporters have chosen to believe chloroquine and hydroxychloroquine do "wonders" for patients or even prevent symptomatic COVID-19 (G1, 2021a; Istoe, 2021). The president even suggested that the drug provokes no adverse reactions (Alves, 2021; Ribeiro, 2021). All this nonsense about chloroquine (CQ) and hydroxychloroquine (HCQ) seems to be associated with preliminary results from *in vitro* studies that have proposed them as possible treatments for COVID-19 (Liu *et al.*, 2020; Yao *et al.*, 2020). Associated to that, data on the efficacy of HCQ and CQ from recent observational studies are inconsistent (COVID-19 RISK and Treatments (CORIST) Collaboration, 2020; Catteau *et al.*, 2020; Lauriola *et al.*, 2020; Lecronier *et al.*, 2020; Magagnoli *et al.*, 2020; Paccoud *et al.*, 2020; Roomi *et al.*, 2020; Rosenberg *et al.*, 2020; Yu *et al.*, 2020; Gao *et al.*, 2020; Geleris *et al.*, 2020; Hong *et al.*, 2020; Kalligeros *et al.*, 2020; Kelly *et al.*, 2021; Kirenga *et al.*, 2020; Kuderer *et al.*, 2020; Lagier *et al.*, 2020). When the first high-quality randomized controlled trials started to appear, the FDA withdrew authorization for emergency use of the technology (Abd-Elsalam *et al.*, 2020). The World Health Organization issued a recommendation against the use of hydroxychloroquine to prevent or treat COVID-19 (Cochrane Collaboration, 2020; World Health Organization, 2020; World Health Organization, 2021). Nevertheless, this discussion is still happening in Brazil, and some health professionals and politicians insist on recommend this drug (Alvim, 2020; Lemos, 2020; Fonseca, 2021; IG Saúde, 2021; Satie, 2021).

This health policy's disastrous conduction in Brazil does not seem to have been caused by lack of information. Some meta-analysis have already been produced on the matter. Of note, a Cochrane Collaboration review did not demonstrate the superiority of chloroquine and hydroxychloroquine for COVID-19 (Singh *et al.*, 2021). Other meta-analyses that included randomized controlled trials and observational studies found the same results (Elavarasi *et al.*, 2020; Fiolet *et al.*, 2021; Kim *et al.*, 2020; Ayele Mega *et al.*, 2020; Sarma *et al.*, 2020; Siemieniuk *et al.*, 2020) despite the inconsistent observational data. All these results seem reasonable; therefore, they should have been incorporated into practice. Nevertheless, they were not. Trying to understand the reason, this study aims to conduct an updated systematic review and meta-analysis of published randomized controlled trials to evaluate the efficacy and safety of chloroquine and hydroxychloroquine (its less toxic metabolite) for the treatment of COVID-19. We included only randomized controlled trials to improve internal validity, guarantee a high level of evidence, and diminish confounding bias.

Methods

A systematic review with meta-analysis was performed to answer the question: is chloroquine and/or hydroxychloro-

quine efficacious and safe for the treatment of COVID-19? The research question in PICO format is available in **Supplementary Materials – Appendix A**. This report followed the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Liberati *et al.*, 2009; Moher *et al.*, 2009; Aromataris *et al.*, 2015). A protocol for this research was published in PROSPERO (CRD42020222685).

Literature search

A systematic search was performed in the databases Medline (*via* PubMed), Embase, The Cochrane Library (in Trials), and Lilacs/Ibecs (*via* BVS) using various descriptors, such as "COVID-19", "coronavirus", "sars-cov-2", "chloroquine" and "hydroxychloroquine". A complementary search was carried out on the references of the included studies, journals specific to the area, conference abstracts, and Google Scholar. The searches were conducted on September 25th, 2020 and updated on February 26th, 2021. The references were imported into EndNote® 7.5 for duplicate removal and transported to the Rayyan QCRI online application (Ouzzani *et al.*, 2016) for the selection process. The search strategies and results by the database are available in **Supplementary Materials – Appendix B.**

Selection criteria and data collection

Randomized controlled trials that compared chloroquine and/or hydroxychloroquine in monotherapy or associated with azithromycin for treatment of COVID-19 were included. There were no restrictions on date, language, or place. Comparisons of hydroxychloroquine with other potentially antiviral drugs (such as remdesivir, ivermectin, lopinavir/ritonavir) were excluded. Studies using particular populations that may have different technology responses due to their severe condition or polypharmacotherapy [such as cancer patients, transplant recipients, and patients with autoimmune diseases (Konig *et al.*, 2020; Kuderer *et al.*, 2020)] were also excluded. In phase 1, references were evaluated for title and abstract. In phase 2, the full texts of the remaining references were retrieved and assessed for inclusion. In phase 3, data were collected regarding the outcomes of interest in a spreadsheet built *a priori* in Microsoft Excel® 2013. Phases 1, 2, and 3 were duplicated by four researchers (AS, AO, EG, and RS) independently, and divergences were resolved by consensus.

Outcomes and data analysis

The primary outcome of the analysis was mortality. Secondary outcomes of interest were "number of cured patients", "number of patients with adverse events", and "number of patients with serious adverse events". Aggregating data from different studies, a qualitative synthesis of results was performed. A quantitative synthesis of clinical outcomes was performed using the inverse variance method adjusting for a random-effects model with the DerSimonian and Laird method (DerSimonian & Laird, 1986; Schwarzer *et al.*, 2015; Higgins *et al.*, 2019b). The associations were presented as relative risks (RR) and 95% confidence intervals (95%CIs). A sensitivity analysis adopting Mantel-Haenszel's RR and Peto's odds ratio (OR) was presented in the supplementary materials. Results with a p-value < 0.05 were considered statistically significant. Analyzes with $I^2 > 30\%$ were assumed to have moderate heterogeneity, $I^2 > 50\%$ as having substantial heterogeneity, and $I^2 > 75\%$ as having high heterogeneity. Heterogeneity data with a p-value of the χ^2-test < 0.10 was considered statistically significant (Higgins *et al.*, 2019b). When convenient, heterogeneity was explored by meta-regression (Baker *et al.*, 2009). The publication bias was assessed by the visual inspection of the funnel plot and by the Egger's test. All analyzes were performed in R (R Core Team, 2020) using the "meta" package (Schwarzer, 2020).

Methodological quality and evidence quality assessment

The Cochrane Collaboration Risk of Bias 2 scale (RoB-2) was used to assess the methodological quality of the included studies (Higgins *et al.*, 2019b; Higgins *et al.*, 2019a). The risk of bias assessment in primary studies was performed in duplicate, and divergent results were reevaluated until a consensus was reached. The Grading of Recommendations Assessment, Development, and Evaluation system (GRADE) was used to evaluate the evidence level. The quality of evidence was classified into four levels: high, moderate, low, and very low (Guyatt *et al.*, 2008a; 2008b; 2008c; 2008d).

Results

Study selection

A total of 2,563 records were extracted from the electronic databases; 22 from an update of the search, and one from other sources. After duplicates removal, 1,967 records were screened, and 1,877 were excluded. The other 90 references were read in full. Of these, 73 were excluded mainly by the type of study (N = 73) and population (N = 13). Seventeen references associated with 16 studies were included in the qualitative and quantitative synthesis (**Figure 1**). Lists of excluded references, randomized controlled trials without results, and included studies are available in **Supplementary Materials – Appendix C to E.**

Description of included studies

Trials from multiple contexts were included in the analysis. The single country analyzes came from China (N = 4), USA and/or Canada (N = 3), Egypt (N = 1), Brazil (N = 1), Taiwan (N = 1), United Kingdom (N = 1), Pakistan (N = 1), Spain (N = 1), Norway (N = 1), and Qatar (N=1). One trial included 30 countries (WHO Solidarity Trial Consortium, 2021). Most studies had small samples (between 30 and 500). The exceptions were the RECOVERY and SOLIDARITY trials with 4,674 and 11,330 participants, respectively (The RECOVERY Collaborative Group, 2020a; WHO Solidarity Trial Consortium, 2021).

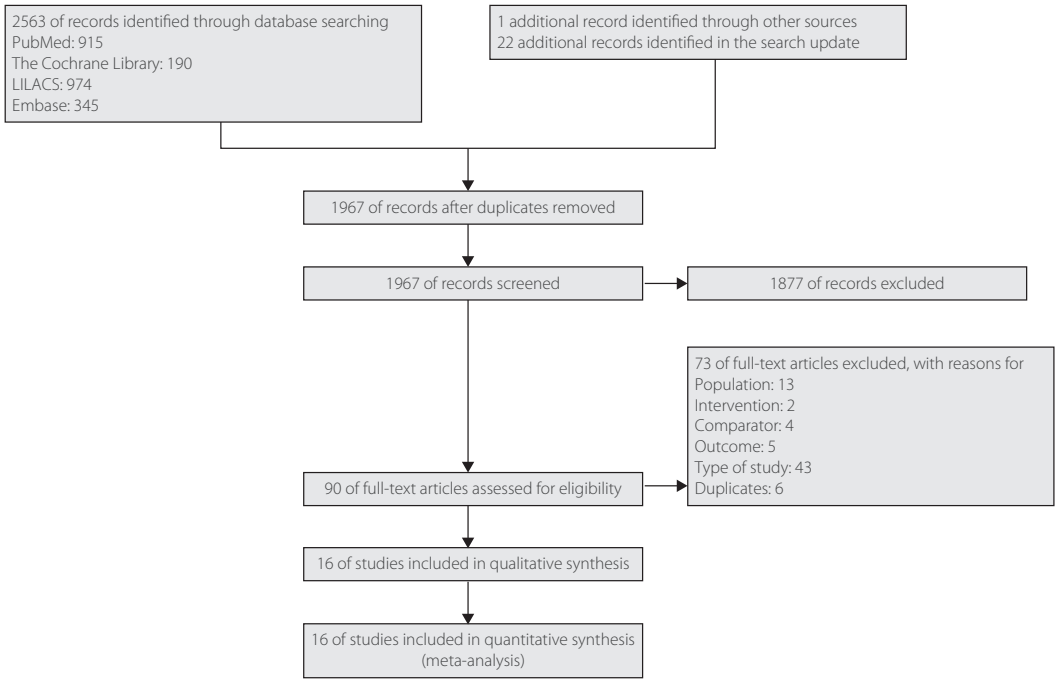

Figure 1. Study flow diagram

The follow-up of most studies was between 14 and 30 days. One study from China and one from Qatar had follow-ups between 5 and 7 days (Chen *et al.*, 2020c; Omrani *et al.*, 2020). None of the studies included only severe patients, 7 included patients in all severity levels, 2 included moderate patients, 5 had mild to moderate patients, and two only included mild patients. The average age of patients varied between 33 (Chen *et al.*, 2020b) and 66 (Ulrich *et al.*, 2020). Only one trial included chloroquine as an intervention (Chen *et al.*, 2020d). This trial also has data on hydroxychloroquine in a separate arm chosen to be a part of the meta-analysis. Therefore, hereon hydroxychloroquine will be treated as "the intervention". The duration of treatment varied between 5 and 21 days (Tang *et al.*, 2020). The loading doses varied between 400 and 2,000 mg/day (Horby *et al.*, 2020; WHO Solidarity Trial Consortium, 2021) and the maintenance doses varied between 400 and 800 mg/day. The characteristics of included studies are available in **Supplementary Materials – Appendix F**.

Qualitative synthesis

Only two studies presented data favorable to the intervention (Chen *et al.*, 2020a; 2020d). Both studies were performed in China, included intermediates outcome in the main analysis – time to clinical response – and found no serious adverse events. Their samples were tiny (N = 62 and N = 48) (Chen *et al.*, 2020a; 2020d), and the follow-up reported in one of them is only five days (Chen *et al.*, 2020a). The daily doses of HCQ are relatively low in both studies (400 mg/day). The other 14 studies neither showed any advantage for HCQ nor demonstrated an increased risk for this group. The largest trials included, SOLIDARITY and RECOVERY, found no difference between HCQ and control in terms of mortality at 28-days (RR = 1.19, 95% CI = 0.89-1.59, p-value = 0.23 and RR = 1.09, 95% CI = 0.97-1.23; p-value = 0.15, respectively) (The RECOVERY Collaborative Group, 2020a; WHO Solidarity Trial Consortium, 2021). The trend observed is in favor of the control in these analyzes. RECOVERY also showed that among the patients who were not mechanically ventilated at baseline, HCQ was associated with a higher frequency of a composite outcome including invasive mechanical ventilation or death than control (30.7% vs. 26.9%; RR = 1.14, 95% CI = 1.03-1.27) (The RECOVERY Collaborative Group, 2020a). Some trials showed an increased risk of adverse events or serious adverse events in patients treated with HCQ, associated or not with azithromycin (Cavalcanti *et al.*, 2020; Mitjà *et al.*, 2020; Skipper *et al.*, 2020; Tang *et al.*, 2020).

Quantitative synthesis

Mortality at the most extended follow-up

Fourteen studies presented data on mortality, but six of these had no deaths during the follow-up. None of the other eight studies showed significant results. Two studies presented data that slightly favor the control [RR = 1.08, 95% CI = 0.97-1.19 (The RECOVERY Collaborative Group, 2020a) and RR = 1.18, CI95% = 0.90-1.56 (WHO Solidarity Trial Consortium, 2021)]. The results of the other studies were very close to the no-effect line or had long confidence intervals. The meta-analysis found no significant difference between intervention and control groups in terms of mortality at the longest follow-up at a 0.05 significance level (RR = 1.09, CI 95% = 0.99-1.19, p-value = 0.08). No heterogeneity was observed ($I^2 = 0\%$,

p-value = 1). The result would be significantly in favor of the control at a 0.10 significance level, though (**Figure 2**). If this result were to be confirmed with more studies, it would have an important clinical meaning against the technology. No difference was found in the sensitivity analysis (**Supplementary Materials – Appendix G and H**).

Cured patients at the most extended follow-up

Seven studies presented data on cured patients. One of them (Abd-Elsalam *et al.*, 2020) significantly favored the intervention (RR = 1.58, CI 95% = 1.13-2.20), but not the others. One study showed data in favor of the control, but not significantly (RR = 0.78, CI 95% = 0.57-1.06) (Omrani *et al.*, 2020). The meta-analysis showed no statistically or clinically significant result (RR = 0.99, IC 95% = 0.89-1.10, p-value = 0.86). The heterogeneity was moderate and non-significant at the limit (I^2 = 44%, p-value = 0.10). Still, all the heterogeneity is associated with only one study (Abd-Elsalam *et al.*, 2020), which is the same study that showed results in favor of the intervention (**Figure 3**). No difference was observed in the sensitivity analysis (**Supplementary Materials – Appendix I and J**).

Adverse events and serious adverse events

Nine studies provided data for the outcome of adverse events. Of these, four showed results that significantly favored the control (Cavalcanti *et al.*, 2020; Mitjà *et al.*, 2020; Skipper *et al.*, 2020; Tang *et al.*, 2020), and the other five did not favor any group. The meta-analysis found that the intervention causes significantly more adverse events than control (RR = 2.28, CI 95% = 1.36-2.83, p-value < 0.01). The heterogeneity in the analysis was high and significant (I^2 = 88%, p-value < 0.01) (**Figure 4**). No substantial difference was observed in the sensitivity analysis (**Supplementary Materials – Appendix K and L**). Curiously, neither total dosage nor daily dosage was associated with the heterogeneity in the meta-regression (**Supplementary Materials – Appendix M**).

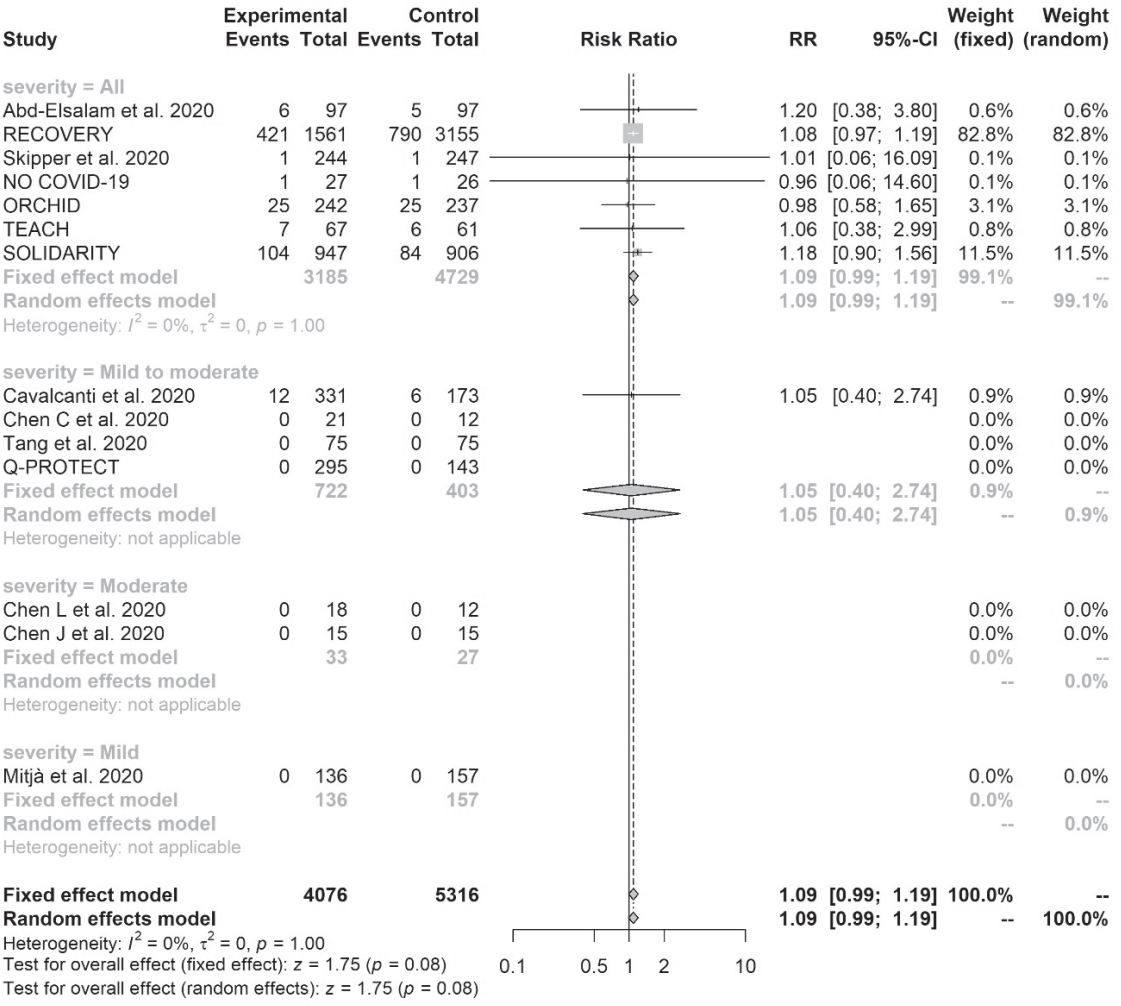

Figure 2. Meta-analysis of mortality at the longest follow-up using the inverse variance method and grouped by severity of cases

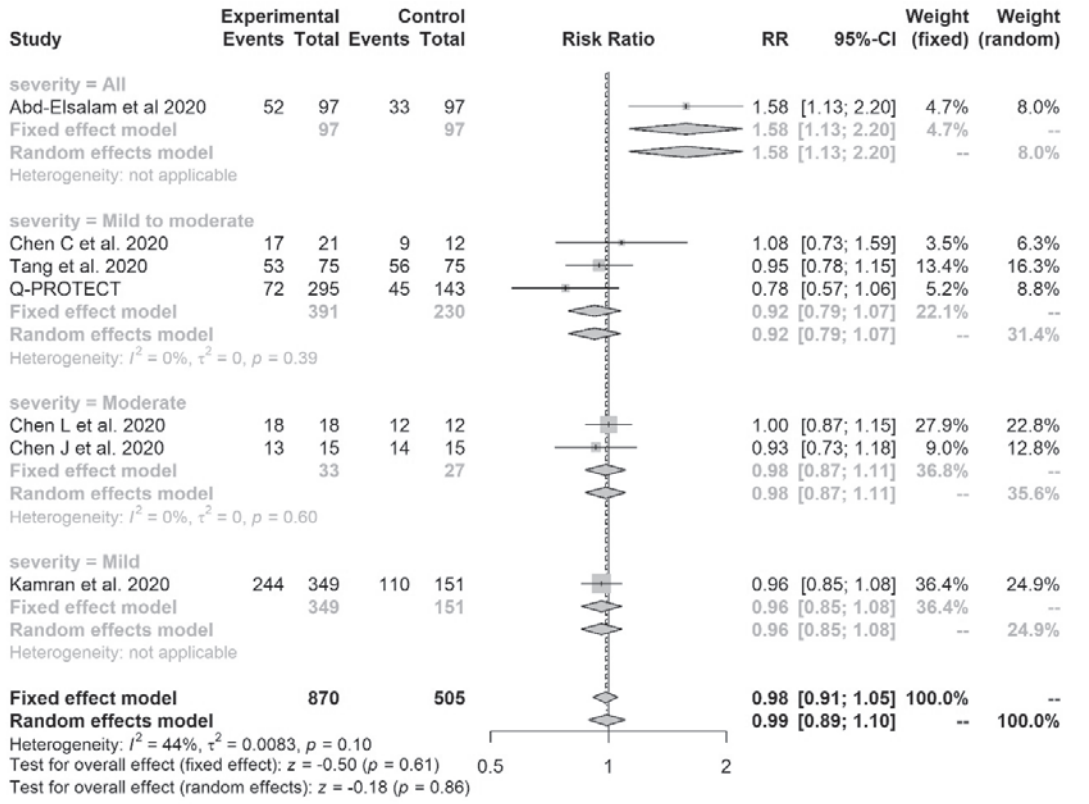

Figure 3. Meta-analysis of cure at the longest follow-up using the inverse variance method and grouped by severity of cases

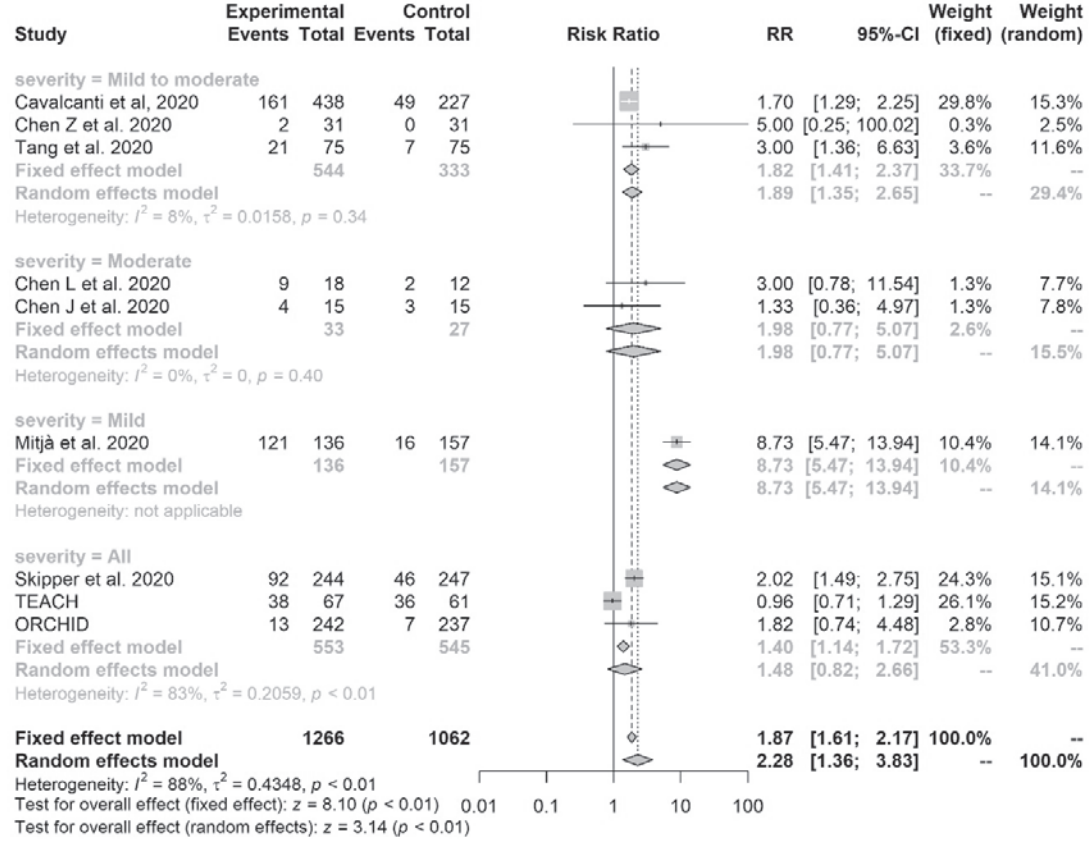

Figure 4. Meta-analysis of adverse events using the inverse variance method and grouped by severity of cases

Eleven studies provided data of serious adverse events, but four of them found no events during follow-up (Chen *et al.*, 2020b; Chen *et al.*, 2020d; Omrani *et al.*, 2020; Skipper *et al.*, 2020). Among the others, only one found significant results favoring the control (Mitjà *et al.*, 2020). The meta-analysis found no difference between the groups (RR = 2.21, CI 95% = 0.89-5.47, p-value = 0.09). This result, as can be seen, would be significant at a 0.10 level and clinically meaningful. The heterogeneity was substantial and significant (I^2 = 66%; p-value < 0.01) (**Figure 5**). Again, neither the total dosage nor daily dosage was associated with the difference between studies in the meta-regression (**Supplementary Materials – Appendix M**).

Quality assessment

The risk of bias assessment was reported by outcome (**Supplementary Materials – Appendix Q**). The most critical outcome included in this analysis was mortality at the most extended follow-up. All three classifications of risk of bias were present for this outcome: low risk of bias (two studies), some concerns (five studies), and high risk of bias (seven studies). Despite that, the quality of evidence was not downgraded for this criterion. In general, the results seem sound and not influenced by bias. The low risk of bias and high risk of bias studies do not seem to have found systematically different results. The same conclusion was reached for severe adverse events. In the case of cure and adverse events, the evidence was downgraded because of bias risk. The general risk of bias assessment is a little worse for these events than for other outcomes. In adverse events, the result might also be more susceptible to changes in studies' methodological quality.

None of the outcomes had enough data for publication bias to be assessed (at least ten studies with data). The funnel plots and Egger's tests are available at **Supplementary Materials – Appendix R to U**. The quality of evidence varied between very low and high. The evidence was the best for the outcome mortality. Therefore, it is unlikely that more data would change this result. On the other hand, the quality of evidence for adverse events and serious adverse events was the lowest. More data on this outcome could improve precision (**Supplementary Materials – Appendix V**).

Discussion

The result of the meta-analyses showed that HCQ does not improve the risk of death (RR = 1.09, CI 95% = 0.99-1.19, p-value = 0.08; 9,392 participants, 14 studies; I^2 = 0%, p-value = 1) or negative PCR at the longest follow-up (RR = 0.99, CI 95% = 0.89-1.10, p-value = 0.86; 1,375 participants, seven studies; I^2 = 44%, p-value = 0.10) among patients with COVID-19. It is associated with more adverse events (RR = 2.28, CI 95%=1.36-

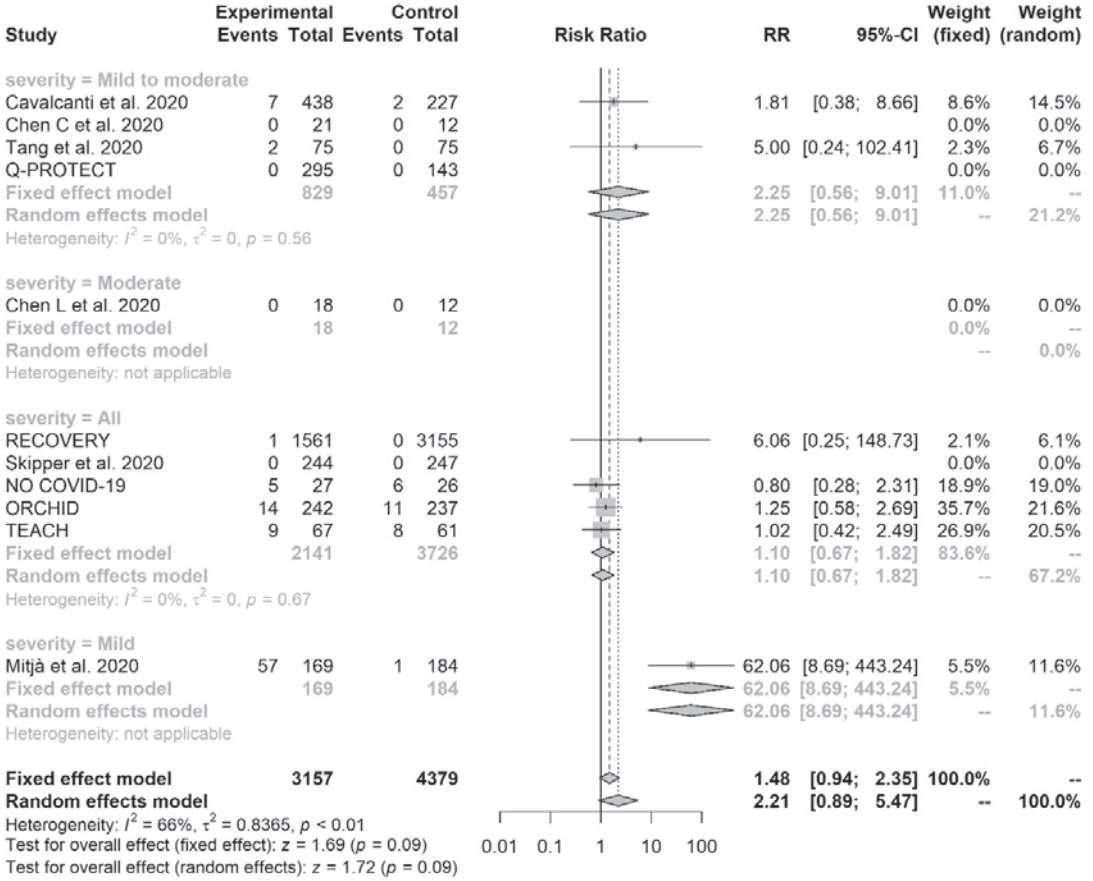

Figure 5. Meta-analysis of serious adverse events using the inverse variance method and grouped by severity of cases

2.83, p-value < 0.01; 2,328 participants, nine studies; $I^2 = 88\%$, p-value < 0.01), but the difference in terms of serious adverse events was not significant at 5% (RR = 2.21, CI 95% = 0.89-5.47, p-value = 0.09; 7,536 participants, 11 studies; $I^2 = 66\%$; p-value < 0.01). In the heterogeneity observed for the outcomes, the difference of dosage between studies could not explain adverse events or serious adverse events. The general quality of evidence varied from very low to high. Except for two particular studies, even the methodologically poorer studies did not suggest the efficacy of hydroxychloroquine to treat patients with COVID-19.

A Cochrane meta-analysis also evaluated the efficacy and safety of HCQ and CQ for the treatment of COVID-19 (Singh *et al.*, 2021). The authors found no difference between the groups regarding mortality (RR = 1.09, CI 95% = 0.99-1.19; 8,208 participants, nine trials) or negative PCR at 14 days (RR = 1.00, CI 95% = 0.91-1.10; 213 participants, three trials). This result is similar to ours, with the only difference that we included more trials. A slight difference was observed in terms of adverse events. The authors of the Cochrane review found the same direction of association we watched, but with a larger magnitude of effect (RR = 2.90, CI 95% = 1.49-5.64; 1,394 participants, six trials). There was, though, an essential difference in terms of serious adverse events. The authors found no difference in this outcome between the groups, like us, but with a different direction of effect (RR = 0.82, CI 95% = 0.37-1.79; 1,004 participants, six trials). Discrepancies in effect's direction are not usual. This difference happened because of additional included studies. Nevertheless, the results of both meta-analyses are very similar. Other meta-analyses that included randomized controlled trials and observational studies found these same results (Elavarasi *et al.*, 2020; Fiolet *et al.*, 2021; Kim *et al.*, 2020; Ayele Mega *et al.*, 2020; Sarma *et al.*, 2020; Siemieniuk *et al.*, 2020).

The literature on hydroxychloroquine and chloroquine for the treatment of COVID-19 varies widely. The study design seems to be a critical factor for this variation. Some observational studies found the technology to be effective for the treatment of COVID-19 patients (COVID-19 RISK and Treatments (CORIST) Collaboration, 2020; Catteau *et al.*, 2020; Hong *et al.*, 2020; Lagier *et al.*, 2020; Lauriola *et al.*, 2020; Mikami *et al.*, 2021; Yu *et al.*, 2020) while others found it to be associated with health damages (Kalligeros *et al.*, 2020; Kelly *et al.*, 2021; Kuderer *et al.*, 2020; Magagnoli *et al.*, 2020; Rosenberg *et al.*, 2020). This huge discordance is not seen among randomized controlled trials (Abd-Elsalam *et al.*, 2020; Chen *et al.*, 2021; Cavalcanti *et al.*, 2020; Kamran *et al.*, 2020; Mitjà *et al.*, 2020; Skipper *et al.*, 2020; Tang *et al.*, 2020; The RECOVERY Collaborative Group, 2020b; 2020a). This stability might be associated with a higher internal validity and better methodological design. The choice of outcome also seems to be essential for the direction of the recommendation made by each study. Most of the favorable results observed in randomized controlled trials come from intermediate outcomes (Chen *et al.*, 2020a; 2020d). Some of the best quality trials, which generally evaluated cure and mortality as outcomes, did not show an advantage for hydroxychloroquine compared to the standard-of-care and, in some cases, the intervention was associated with adverse effects (Horby *et al.*, 2020; Mitjà *et al.*, 2020; The RECOVERY Collaborative Group, 2020a; WHO Solidarity Trial Consortium, 2021).

The methods of treatment and prevention of COVID-19 are urgent problems that societies are trying to deal with. The prevention of COVID-19 and the reduction of mortality would be adequately achieved through one of the several vaccines that are reaching the market (Baden *et al.*, 2020; Polack *et al.*, 2020; Voysey *et al.*, 2021). However, treatments are and will be necessary for patients already infected, residual cases after herd immunity, or in case of a future epidemic. There is no universally accepted treatment for COVID-19 and chloroquine, and hydroxychloroquine are ineffective and unsafe for treating the disease. Some trials evaluating these drugs have even been terminated early for futility (Self *et al.*, 2020); i.e., the interim analysis showed an inability of studies to achieve statistical significance (Snapinn *et al.*, 2006). Brazil has spent millions of BRL producing and purchasing chloroquine and hydroxychloroquine for these patients without any proof of efficacy, which even led to internal investigations (Confederação Nacional dos Trabalhadores da Saúde, 2020; Fiorio, 2020; Junqueira, 2020; Colaboração para o UOL, 2021; Shalders, 2021; Teófilo & Cardim, 2021).

The follow-up of patients in the included studies was concise, ranging from 5 to 28 days. If there were a change in the outcomes after this period, these studies would not have captured it; e. g., if the intervention reduced long-term mortality associated with complications from the disease. There is some distancing of some studies from the final, and most important, outcomes. Some studies focus on evaluating secondary results that may not be the most relevant for this evaluation. It did not have to be this way. Intermediate outcomes are crucial in evaluations of technologies requiring many participants or taking an extended follow-up. The scenario of COVID-19 is neither. Results happen in a relatively short follow-up, and they are not rare. One problem in adopting outcomes might have been the tiny samples of some studies.

There is no evidence that hydroxychloroquine reduces the risk of death or improves cure rates in patients with COVID-19. The drugs might also be associated with an increased risk of adverse events and serious adverse events. The quality of the evidence is reasonable for the efficacy outcomes and relatively insufficient for the safety outcomes. Since the efficacy of the intervention was not demonstrated and the quality of evidence was high or moderate, it is unlikely that the results would favor the intervention if more patients were to be randomized.

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Yu B, Li C, Chen P, Zhou N, Wang L, Li J, et al. Low dose of hydroxychloroquine reduces fatality of critically ill patients with COVID-19. Sci China Life Sci. 2020;63(10):1515-21.

APPENDICES

Appendix A. Research question in PICO format

P – Population	Patients with COVID-19.
I – Intervention	Therapeutic regimens that use hydroxychloroquine or chloroquine
C – Comparator	Placebo or standard-of-care (SOC)
O – Outcomes	Mortality, cure, and adverse events
S – Setting	Any
Type of study	Randomized controlled trials

Appendix B. Search strategy

Database	Strategy	#
PubMed	((((((((((((((COVID-19[Supplementary Concept]) OR (COVID-19[Title/Abstract])) OR (2019 novel coronavirus disease[Title/Abstract])) OR (COVID19[Title/Abstract])) OR (COVID-19 pandemic[Title/Abstract])) OR (SARS-CoV-2 infection[Title/Abstract])) OR (COVID-19 virus disease[Title/Abstract])) OR (2019 novel coronavirus infection[Title/Abstract])) OR (2019-nCoV infection[Title/Abstract])) OR (coronavirus disease 2019[Title/Abstract])) OR (coronavirus disease-19[Title/Abstract])) OR (2019-nCoV disease[Title/Abstract])) OR (COVID-19 virus infection[Title/Abstract])) AND ((((((((((((((((((((Chloroquine[MeSH Terms]) OR (Chloroquine[Title/Abstract])) OR (Chlorochin[Title/Abstract])) OR (Chingamin[Title/Abstract])) OR (Khingamin[Title/Abstract])) OR (Nivaquine[Title/Abstract])) OR (Chloroquine Sulfate[Title/Abstract])) OR (Sulfate, Chloroquine[Title/Abstract])) OR (Chloroquine Sulphate[Title/Abstract])) OR (Sulphate, Chloroquine[Title/Abstract])) OR (Aralen[Title/Abstract])) OR (Arequin[Title/Abstract])) OR (Arechine[Title/Abstract])) OR (Hydroxychloroquine[MeSH Terms])) OR (Hydroxychloroquine[Title/Abstract])) OR (Oxychlorochin[Title/Abstract])) OR (Oxychloroquine[Title/Abstract])) OR (Hydroxychlorochin[Title/Abstract])) OR (Plaquenil[Title/Abstract])) OR (Hydroxychloroquine Sulfate[Title/Abstract]))) AND ((("Cohort Studies"[MeSH Terms] OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("cohort"[All Fields] AND "study"[All Fields])) OR "cohort study"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("studies"[All Fields] AND "cohort"[All Fields])) OR "studies cohort"[All Fields]) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("study"[All Fields] AND "cohort"[All Fields])) OR "study cohort"[All Fields]) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("concurrent"[All Fields] AND "studies"[All Fields])) OR "concurrent studies"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("studies"[All Fields] AND "concurrent"[All Fields])) OR "studies concurrent"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("concurrent"[All Fields] AND "study"[All Fields])) OR "concurrent study"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("study"[All Fields] AND "concurrent"[All Fields])) OR "study concurrent"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("historical"[All Fields] AND "cohort"[All Fields] AND "studies"[All Fields])) OR "historical cohort studies"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("studies"[All Fields] AND "historical"[All Fields] AND "cohort"[All Fields])) OR "studies historical cohort"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("cohort"[All Fields] AND "studies"[All Fields] AND "historical"[All Fields]))) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("cohort"[All Fields] AND "study"[All Fields] AND "historical"[All Fields])) OR "cohort study historical"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("historical"[All Fields] AND "cohort"[All Fields] AND "study"[All Fields])) OR "historical cohort study"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("study"[All Fields] AND "historical"[All Fields] AND "cohort"[All Fields])) OR "study historical cohort"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("analysis"[All Fields] AND "cohort"[All Fields])) OR "analysis cohort"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("analysis"[All Fields] AND "cohort"[All Fields])) OR "analysis cohort"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("cohort"[All Fields] AND "analyses"[All Fields])) OR "cohort analyses"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("cohort"[All Fields] AND "analysis"[All Fields])) OR "cohort analysis"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("closed"[All Fields] AND "cohort"[All Fields] AND "studies"[All Fields])) OR "closed cohort studies"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("cohort"[All Fields] AND "studies"[All Fields] AND "closed"[All Fields]))) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("closed"[All Fields] AND "cohort"[All Fields] AND "study"[All Fields])) OR "closed cohort study"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("cohort"[All Fields] AND "study"[All Fields] AND "closed"[All Fields]))) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("study"[All Fields] AND "closed"[All Fields] AND "cohort"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("studies"[All Fields] AND "closed"[All Fields] AND "cohort"[All Fields]))) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("incidence"[All Fields] AND "studies"[All Fields])) OR "incidence studies"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("incidence"[All Fields] AND "study"[All Fields])) OR "incidence study"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("studies"[All Fields] AND "incidence"[All Fields])) OR "studies incidence"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("study"[All Fields] AND "incidence"[All Fields])) OR "study incidence"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR "cohort"[All Fields] OR "cohort s"[All Fields] OR "cohorte"[All Fields] OR "cohorts"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort Studies"[All Fields] OR ("cohort"[All Fields] AND "analysis"[All Fields])) OR "cohort analysis"[All Fields])) OR ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields])) OR "Cohort	915

Database	Strategy	#
	Studies"[All Fields] OR ("cohort"[All Fields] AND "study"[All Fields]) OR "cohort study"[All Fields]) OR (("Longitudinal Studies"[MeSH Terms] OR ("longitudinal"[All Fields] AND "studies"[All Fields]) OR "Longitudinal Studies"[All Fields] OR "prospective"[All Fields] OR "prospectively"[All Fields]) AND ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields]) OR "Cohort Studies"[All Fields] OR "cohort"[All Fields] OR "cohort s"[All Fields] OR "cohorte"[All Fields] OR "cohorts"[All Fields])) OR (("Retrospective Studies"[MeSH Terms] OR ("retrospective"[All Fields] AND "studies"[All Fields]) OR "Retrospective Studies"[All Fields] OR "retrospective"[All Fields] OR "retrospectively"[All Fields] OR "retrospectives"[All Fields]) AND ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields]) OR "Cohort Studies"[All Fields] OR "cohort"[All Fields] OR "cohort s"[All Fields] OR "cohorte"[All Fields] OR "cohorts"[All Fields])) OR (("Retrospective Studies"[MeSH Terms] OR ("retrospective"[All Fields] AND "studies"[All Fields]) OR "Retrospective Studies"[All Fields] OR "retrospective"[All Fields] OR "retrospectively"[All Fields] OR "retrospectives"[All Fields]) AND ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields]) OR "Cohort Studies"[All Fields] OR ("cohort"[All Fields] AND "study"[All Fields]) OR "cohort study"[All Fields])) OR (("Longitudinal Studies"[MeSH Terms] OR ("longitudinal"[All Fields] AND "studies"[All Fields]) OR "Longitudinal Studies"[All Fields] OR "prospective"[All Fields] OR "prospectively"[All Fields]) AND ("Cohort Studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields]) OR "Cohort Studies"[All Fields] OR ("cohort"[All Fields] AND "study"[All Fields]) OR "cohort study"[All Fields])) OR "Follow-Up Studies"[MeSH Terms] OR ("Follow-Up Studies"[MeSH Terms] OR ("follow up"[All Fields] AND "studies"[All Fields]) OR "Follow-Up Studies"[All Fields] OR ("follow"[All Fields] AND "up"[All Fields] AND "studies"[All Fields]) OR "Follow-Up Studies"[All Fields]) OR ("Follow-Up Studies"[MeSH Terms] OR ("follow up"[All Fields] AND "studies"[All Fields]) OR "Follow-Up Studies"[All Fields] OR ("follow"[All Fields] AND "up"[All Fields] AND "study"[All Fields]) OR "follow up study"[All Fields]) OR ("Follow-Up Studies"[MeSH Terms] OR ("follow up"[All Fields] AND "studies"[All Fields]) OR "Follow-Up Studies"[All Fields] OR ("cohort"[All Fields] AND "follow"[All Fields] AND "up"[All Fields]) OR "cohort follow up"[All Fields]) OR "studies follow up"[All Fields]) OR ("Follow-Up Studies"[MeSH Terms] OR ("follow up"[All Fields] AND "studies"[All Fields]) OR "Follow-Up Studies"[All Fields] OR ("study"[All Fields] AND "follow"[All Fields] AND "up"[All Fields]) OR "study follow up"[All Fields]) OR ("Follow-Up Studies"[MeSH Terms] OR ("follow up"[All Fields] AND "studies"[All Fields]) OR "Follow-Up Studies"[All Fields] OR ("followup"[All Fields] AND "studies"[All Fields]) OR "followup studies"[All Fields]) OR ("Follow-Up Studies"[MeSH Terms] OR ("follow up"[All Fields] AND "studies"[All Fields]) OR "Follow-Up Studies"[All Fields] OR ("followup"[All Fields] AND "study"[All Fields]) OR "followup study"[All Fields]) OR ("Follow-Up Studies"[MeSH Terms] OR ("follow up"[All Fields] AND "studies"[All Fields]) OR "Follow-Up Studies"[All Fields] OR ("studies"[All Fields] AND "followup"[All Fields]) OR "studies followup"[All Fields]) OR ("Follow-Up Studies"[MeSH Terms] OR ("follow up"[All Fields] AND "studies"[All Fields]) OR "Follow-Up Studies"[All Fields] OR ("study"[All Fields] AND "followup"[All Fields]) OR "study followup"[All Fields]) OR ("Epidemiologic Studies"[MeSH Terms] OR "Cross-Sectional Studies"[MeSH Terms] OR "Retrospective Studies"[MeSH Terms] OR "Longitudinal Studies"[MeSH Terms] OR "Prospective Studies"[MeSH Terms])) OR (("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]))	
The Cochrane Library	Search Name: COVID-19 (Trials) - Chlor Last Saved: 25/09/2020 11:46:31 Comment: ID Search #1 MeSH descriptor: [Coronavirus] explode all trees #2 MeSH descriptor: [Chloroquine] explode all trees #3 MeSH descriptor: [Hydroxychloroquine] explode all trees #4 COVID-19 #5 COVID #6 COVID19 #7 corona #8 corona* #9 #8 AND #2 #10 #2 OR #3 #11 #1 OR #4 OR #5 OR #6 OR #7 OR #8 #12 #10 AND #11	190
The Cochrane Library COVID-19 Study Registry	chloroquine OR hydroxychloroquine	974
Embase	('coronavirus disease 2019'/exp OR '2019-ncov disease' OR '2019-ncov infection' OR 'covid 19' OR 'covid 2019' OR 'covid19' OR 'Wuhan coronavirus disease' OR 'Wuhan coronavirus infection' OR 'coronavirus disease 2019' OR 'ncov 2019 disease' OR 'ncov 2019 infection' OR 'novel coronavirus 2019 disease' OR 'novel coronavirus 2019 infection' OR 'novel coronavirus disease 2019' OR 'novel coronavirus infection 2019') AND ('chloroquine'/exp OR '4 (4 diethylamino 1 methylbutylamine) 7 chlorchinolin diphosphate' OR '4 (4 diethylamine 1 methylbutylamine) 7 chlorchinolin sulfate' OR '4 (4 diethylamino 1 methylbutylamine) 7 chlorchinolin sulphate' OR '4 (4 diethylamino 1 methylbutylamine) 7 chloroquinoline' OR '7 chloro 4 (4 diethylamino 1 methylbutylamine) quinoline' OR '7 chloro 4 (4 diethylamino 1 methylbutylamine) quinoline diphosphate' OR 'a-cq' OR 'amokin' OR 'amokine' OR 'anoclor' OR 'aralan' OR 'aralen' OR 'aralen hydrochloride' OR 'aralen phosphate' OR 'aralene' OR 'arechin' OR 'arechine' OR 'arequine' OR 'arthrochin' OR 'arthrochine' OR 'arthroquine' OR 'artrichin' OR 'artrichine' OR 'artriquine' OR 'avloclor' OR 'avoclor' OR 'bemaphata' OR 'bemaphate' OR 'bemasulph' OR 'bipiquin' OR 'cadiquin' OR 'chemochin' OR 'chemochine' OR 'chingamine' OR 'chingaminum' OR 'chloraquine' OR 'chlorochin' OR 'chlorochine' OR 'chlorofoz' OR 'chloroquin' OR 'chloroquin phosphate' OR 'chloroquine' 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 'chloroquinidiphosphas' OR 'chloroquinumdiphosphoricum' OR 'chlorquin' OR 'chlorquine' OR 'choloquine' OR 'choroquine sulfate' OR 'choroquine sulphate' OR 'cidanchin' OR 'clo-kit junior' OR 'clorichina' OR 'clorichine' OR 'cloriquine' OR 'clorochina' OR 'delagil' OR 'delagyl' OR 'dichinalex' OR 'diclokin' OR 'diquinalex' OR 'diroquine' OR 'emquin' OR 'genocin' OR 'gontochin' OR 'gontochine' OR 'gontoquine' OR 'heliopar' OR 'imagon' OR 'iroquine' OR 'klorokin' OR 'klorokine' OR 'klorokinfosfat' OR 'lagaquin' OR 'malaquin' OR 'malarex' OR 'malarivon' OR 'malaviron' OR 'maliaquine' OR 'maquine' OR 'mesylith' OR 'mexaquin' OR 'mirquin' OR 'nivachine' OR 'nivaquin' OR 'nivaquine' OR 'nivaquine (b)' OR 'nivaquine b' OR 'nivaquinedp' OR 'nivaquine forte' OR 'p roquine' OR 'quinachlor' OR 'quingamine' OR 'repal' OR 'resochen' OR 'resochene' OR 'resochin' OR 'resochin junior' OR 'resochina' OR 'resochine' OR 'resochinon' OR 'resoquina' OR 'resoquine' OR 'reumachlor' OR 'roquine' OR 'rp 3377' OR 'rp3377' OR 'sanoquin' OR 'sanoquine' OR 'silbesan' OR 'siragan' OR 'sirajan' OR 'sn 7618' OR 'sn7618' OR 'solprina' OR 'solprine' OR 'tresochin' OR 'tresochine' OR 'tresoquine' OR 'trochin' OR 'trochine' OR 'troquine' OR 'w 7618' OR 'w7618' OR 'win 244' OR 'win244' OR 'hydroxychloroquine'/exp OR '7 chloro 4 [4 [ethyl (2 hydroxyethyl) amino] 1 methylbutylamine] quinoline' OR '7 chloro 4 [4 [ethyl (2 hydroxyethyl) amino] 1 methylbutylamine] quinoline diphosphate' OR 'apo-hydroxychloroquine' OR 'chloroquinol' OR 'ercoquin' OR 'hydrochloroquine' OR 'hydrocloroquine' OR 'hydroxychloroquine' OR 'oxychloroquine' OR 'quensyl' OR 'sn 8137') AND ('randomized controlled trial'/exp OR 'controlled trial, randomized' OR 'randomized controlled study' OR 'randomized controlled trial' OR 'randomized controlled study' OR 'randomized controlled trial' OR 'trial, randomized controlled' OR 'cohort analysis'/exp OR 'analysis, cohort' OR 'cohort analysis' OR 'cohort fertility' OR 'cohort life cycle' OR 'cohort studies' OR 'cohort study' OR 'fertility, cohort')	345

Database	Strategy	#
Lilacs	(tw:((tw:(COVID-19)) OR (tw:(COVID19)) OR (tw:(COVID*)) OR (tw:(corona*)) OR (tw:(sars-cov-2)))) AND (tw:((tw:(chloroquine)) OR (tw:(hydroxychloroquine)) OR (tw:(cloroquina)) OR (tw:(hidroxicloroquina))))	138
Contribution from other sources		1
Snowballing		0
Total		2563
Total after duplicate removals		1945
References in phase II		58
Included references		10
New references assessed for updates		327
New references included		7
Total number of included references		17
Total number of included studies		16

Appendix C. List of references excluded in phase II

#	Study	Reason
1	EudraCT 2020-001536-98. Prophylaxis of COVID-19 infection with hydroxychloroquine in healthcare. 2020. https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001536-98/ES/	O – No results
2	TANG, W. *et al.* Hydroxychloroquine in patients mainly with mild to moderate COVID-19: an open-label, randomized, controlled trial. Medrxiv, 2020. DOI: https://doi.org/10.1101/2020.04.10.20060558	Results are included in another article (ID64)
3	Lother, S. A. *et al.* Post-exposure Prophylaxis or Preemptive Therapy for SARS-Coronavirus-2: Study Protocol for a Pragmatic Randomized Controlled Trial.2020. DOI: https://doi.org/10.1101/2020.05.01.20087999	Study equal to ID49-Protocol (NCT04308668)
4	Holubar, j. *et al.* Monitoring of patients with systemic lupus erythematosus during the COVID-19 outbreak. Annals of the Rheumatic Diseases, 2020. DOI:10.1136/annrheumdis-2020-217919	P – Specific population
5	Luo, J., *et al.* COVID-19 in patients with lung cancer. Ann Oncol., v.31, n.10, p.1386-1396, 2020. DOI:10.1016/j.annonc.2020.06.007.	O – treatment with hydroxychloroquine is not the research target
6	Ferreira, a.; OLIVEIRA-E-SILVA, A.; BETTENCOURT, P. Chronic treatment with hydroxychloroquine and SARS-CoV-2 infection. Journal of Medical Virology, 2020. DOI:10.1002/jmv.26286	P – patients evaluated with COVID who received the intervention as a chronic treatment
7	NCT04491994. Clearing the Fog: Is Hydroxychloroquine Effective in Reducing COVID-19 Progression (COVID-19) - *Full Text View - ClinicalTrials.gov* (n.d.). Retrieved November 02, 2020, from https://clinicaltrials.gov/ct2/show/NCT04491994	The study protocol included
8	Davido, b. *et al.* Impact of medical care including anti-infective agents use on the prognosis of COVID-19 hospitalized patients over time. International Journal of Antimicrobial Agents, 2020. DOI:10.1016/j.ijantimicag.2020.106129	C – The study does not have any comparison arm within the requirements of this review.
9	Kalligeros, M. *et al.* Hydroxychloroquine use in hospitalised patients with COVID-19: An observational matched cohort study. J Glob Antimicrob Resist., v. 22, p.842-844, 2020. DOI:10.1016/j.jgar.2020.07.018	Results included in another article (ID 41)
10	Roomi, S. *et al.* Efficacy of Hydroxychloroquine and Tocilizumab in Patients With COVID-19: Single-Center Retrospective Chart Review. J Med Internet Res., v. 22, n. 9, 2020. DOI:10.2196/21758	Duplicate
11	Zhong, j. *et al.* COVID-19 in patients with rheumatic disease in Hubei province, China: a multicentre retrospective observational study. Lancet Rheumatol., v. 2, n. 9, p.e557-e564, 2020. DOI:10.1016/S2665-9913(20)30227-7	P – Specific population
12	Sem, S.; Werner, a.; Shekhar, a. Within a large healthcare system, the incidence of positive COVID-19 results and mortality are lower in patients on chronic hydroxychloroquine therapy. Drugs TherPerspect., v. 36, p. 298–299. 2020. DOI: 10.1007/s40267-020-00741-x	P – Patients evaluated with COVID-19 who received the intervention as a chronic treatment
13	Rentsch, C. T. *et al.* Hydroxychloroquine for prevention of COVID-19 mortality: a population-based cohort study. MedRxiv, 2020. DOI: https://doi.org/10.1101/2020.09.04.20187781.	P – The evaluated patients were continuously using the intervention before the COVID-19 outbreak to treat rheumatoid arthritis and systemic lupus.
14	Bhandari, s. *et al.* Characteristics, Treatment Outcomes and Role of Hydroxychloroquine among 522 COVID-19 hospitalized patients in Jaipur City: An Epidemio-Clinical Study. The Journal of the Association of Physicians of India, v. 68, n. 6, p. 13–19, 2020.	P – The effect of hydroxychloroquine was evaluated in asymptomatic patients.

#	Study	Reason
15	Bhuyan, M. A. *et al.* Treatment of COVID-19 Patients at a Medical College Hospital in Bangladesh. Euroasian journal of hepato-gastroenterology, v. 10, n. 1, p. 27–30, 2020. DOI: 10.5005/jp-journals-10018-1317	C – There is no comparator. All patients received a hydroxychloroquine regimen.
16	Borobia, a.m *et al.* A Cohort of Patients with COVID-19 in a Major Teaching Hospital in Europe. Journal of Clinical Medicine, 2020.DOI: 10.3390/jcm9061733.	C – The study does not have any comparison arm within the requirements of this review.
17	CASTELNUOVO A. D., *et al.* Use of hydroxychloroquine in hospitali-sed COVID-19 patients is associated with reduced mortality: Findings from the observational multicentre Italian CORIST study. European journal of internal medicine, 2020. DOI: https://doi.org/10.1016/j.ejim.2020.08.019	C – Patients receiving HCQ probably received another drug for COVID-19 treatment (lopinavir/ritonavir or darunavir/cobicistat, remdesivir, tocilizumab or sarilumab, corticosteroids)
18	Chatterjee P., *et al.* Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19. Indian J Med Res. v. 151, n. 5, p. 459-467, 2020. DOI:10.4103/ijmr.IJMR_2234_20	S – Case-control study
19	Franco, j. V. A. La hidroxicloroquina no reduciríalaportación viral delnuevocoronavirus (COVID-19). Evid. actual. práct. Ambul., v.23, n.1, 2020.	S – Comment
20	Konig M., *et al.* Baseline use of hydroxychloroquine in systemic lupus erythematosus does not preclude SARS-CoV-2 infection and severe COVID-19. Ann Rheum Dis., v.79, n.10, p. 1386-1388, 2020.	O – It does not present data regarding exposed and non-exposed individuals who did or did not develop the disease. It is also about a particular subgroup of patients who may respond differently to therapy against COVID.
21	Kuderer n. M., *et al.* Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lance,v. 395, n. 10241, p.1907-1918, 2020. DOI: https://doi.org/10.1016/S0140-6736(20)31187-9	P – These patients are being excluded because it is not possible to evaluate the use of the drug in this population. In addition, several confounders specific to the cancer population may make it difficult to aggregate the data with other studies. It will be commented on in the discussion but will not be included in the results to assess the usefulness of CQ/HCQ for COVID-19 treatment.
22	Lother S. A. *et al.* Post-exposure prophylaxis or pre-emptive therapy for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): study protocol for a pragmatic randomized-controlled trial. Can J Anaesth, v.67, n.9, p.1201-1211, 2020. DOI: 10.1007/s12630-020-01684-7	P – No results
23	NCT04421664. Preemptive Therapy for SARS-Coronavirus-2 (COVID-19 PEP Canada).2020. https://clinicaltrials.gov/show/NCT04421664	The study protocol included
24	NCT04308668. Post-exposure Prophylaxis for SARS-Coronavirus-2. 2020. https://clinicaltrials.gov/show/NCT04308668	The study protocol included
25	NCT04332991. Outcomes Related to COVID-19 Treated With Hydroxychloroquine Among In-patients With Symptomatic Disease. 2020. https://clinicaltrials.gov/show/NCT04332991	O – It seems the results are not published.
26	NCT04384380. Efficacy and Tolerability of Hydroxychloroquine in Adult Patients With COVID-19. 2020. https://clinicaltrials.gov/show/NCT04384380	O – It seems the results are not published.
27	NCT04322123. Safety and Efficacy of Hydroxychloroquine Associated With Azithromycin in SARS-Cov-2 Virus.2020. https://clinicaltrials.gov/show/NCT04322123	I/C – All arms have HCQ.
28	Rivera, d. R. *et al.* Utilization of COVID-19 Treatments and Clinical Outcomes among Patients with Cancer: A COVID-19 and Cancer Consortium (CCC19) Cohort Study. Cancer Discov, v. 10, n. 10, p. 1514-1527. DOI: 10.1158/2159-8290. CD-20-0941	P – These patients are being excluded because it is not possible to evaluate the drug use in this population. In addition, several confounders specific to the cancer population may make it difficult to aggregate the data with other studies. It will be commented on in the discussion but will not be included in the results to assess the CQ/HCQ's usefulness for COVID-19 treatment.
29	Roomi, S. *et al.* Efficacy of Hydroxychloroquine and Tocilizumab in Patients With COVID-19: Single-Center Retrospective Chart Review. J Med Internet Res, v. 22, n. 9, p.e21758, 2020.	I/C – The intervention and comparator groups are not well delimited. I mean, they can have patients with HCQ and T, just HCQ, just T, neither of them. They have just assessed HCQ vs. without HCQ and T vs. without T.
30	Sharma, p. *et al.* COVID-19 Outcomes Among Solid Organ Transplant Recipients: A Case-Control Study. Transplantation, 2020. DOI: 10.1097/tp.0000000000003447	P – These patients are being excluded because it is not possible to evaluate the drug use in this population. In addition, several confounders specific to the transplant population may make it difficult to aggregate the data with other studies. It will be commented on in the discussion but will not be included in the results to assess the CQ/HCQ's usefulness for COVID-19 treatment.
31	Yadaw, A. S. *et al.* Clinical predictors of COVID-19 mortality. medRxiv.2020. DOI:https://doi.org/10.1101/2020.05.19.20103036	S – Machine learning study considering the use of HCQ as an outcome predictor
32	Geleris, joshua *et al.* Observational study of hydroxychloroquine in hospitalized patients with Covid-19. New England Journal of Medicine, v. 382, n. 25, p. 2411-2418, 2020.	I/C – Both groups use AZ
33	Albani, Filippo *et al.* Impact of azithromycin and/or hydroxychloroquine on hospital mortality in COVID-19. Journal of clinical medicine, v. 9, n. 9, p. 2800, 2020.	S
34	Arshad, samia *et al.* Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. International journal of infectious diseases, v. 97, p. 396-403, 2020.	S
35	Bernardini, Andrea *et al.* Assessing QT interval in COVID-19 patients: safety of hydroxychloroquine-azithromycin combination regimen. International Journal of Cardiology, v. 324, p. 242-248, 2021.	S

#	Study	Reason
36	Bhattacharya, r. *et al.* Pre exposure Hydroxychloroquine use is associated with reduced COVID19 risk in healthcare workers. medRxiv 2020: 2020.06. 09.20116806. Epub June, v. 12.	S
37	Boulware, David R. *et al.* A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. New England Journal of Medicine, v. 383, n. 6, p. 517-525, 2020.	S
38	Catteau, lucy *et al.* Low-dose hydroxychloroquine therapy and mortality in hospitalized patients with COVID-19: a nationwide observational study of 8075 participants. International journal of antimicrobial agents, v. 56, n. 4, p. 106144, 2020.	S
39	Fried, Michael W. *et al.* Patient characteristics and outcomes of 11,721 patients with COVID19 hospitalized across the United States. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America, 2020.	S
40	Gao, guiju *et al.* Brief Report: Retrospective Evaluation on the Efficacy of Lopinavir/Ritonavir and Chloroquine to Treat Nonsevere COVID-19 Patients. Journal of acquired immune deficiency syndromes (1999), v. 85, n. 2, p. 239, 2020.	S
41	Gautret, Philippe *et al.* Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International journal of antimicrobial agents, v. 56, n. 1, p. 105949, 2020.	S
42	Ip, andrew *et al.* Hydroxychloroquine and tocilizumab therapy in COVID-19 patients—An observational study. PloS one, v. 15, n. 8, p. e0237693, 2020.	S
43	Kalligeros, Markos *et al.* Hydroxychloroquine use in hospitalized patients with COVID-19: An observational matched cohort study. Journal of global antimicrobial resistance, v. 22, p. 842-844, 2020.	S
44	Kelly, mary *et al.* Clinical outcomes and adverse events in patients hospitalized with COVID-19, treated with off-label hydroxychloroquine and azithromycin. British journal of clinical pharmacology, v. 87, n. 3, p. 1150-1154, 2021.	S
45	Kirenga, Bruce *et al.* Characteristics and outcomes of admitted patients infected with SARS-CoV-2 in Uganda. BMJ open respiratory research, v. 7, n. 1, p. e000646, 2020.	S
46	Lagier, jean-christophe *et al.* Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis. Travel medicine and infectious disease, v. 36, p. 101791, 2020.	S
47	Lauriola, M. *et al.* Effect of combination therapy of hydroxychloroquine and azithromycin on mortality in COVID-19 patients. Clinical and Translational Science, 2020.	S
48	Lecronier, marie *et al.* Comparison of hydroxychloroquine, lopinavir/ritonavir, and standard of care in critically ill patients with SARS-CoV-2 pneumonia: an opportunistic retrospective analysis. Critical Care, v. 24, n. 1, p. 1-9, 2020.	S
49	Magagnoli, joseph *et al.* Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. Med, v. 1, n. 1, p. 114-127. e3, 2020.	S
50	Mahévas, matthieu *et al.* Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. Bmj, v. 369, 2020.	S
51	Mitja, O. *et al.* A Cluster-Randomized Trial of Hydroxychloroquine as Prevention of Covid-19 Transmission and Disease. medRxiv 2020: 2020.07. 20.20157651. Epub http://doi. org/10.1101/2020.07, v. 20.	S
52	Paccoud, olivier *et al.* Compassionate use of hydroxychloroquine in clinical practice for patients with mild to severe Covid-19 in a French university hospital. Clinical Infectious Diseases, 2020.	S
53	Rajasingham, R. *et al.* Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: a randomized trial. medRxiv 2020: 2020.09. 18.20197327. Epub http://doi. org/10.1101/2020.09, v. 18.	S
54	Rosenberg, eli s. *et al.* Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. Jama, v. 323, n. 24, p. 2493-2502, 2020.	S
55	Sbidian, Emilie *et al.* Hydroxychloroquine with or without azithromycin and in-hospital mortality or discharge in patients hospitalized for COVID-19 infection: a cohort study of 4,642 in-patients in France. MedRxiv, 2020.	S
56	Yu, bo *et al.* Low dose of hydroxychloroquine reduces fatality of critically ill patients with COVID-19. Science China Life Sciences, v. 63, n. 10, p. 1515-1521, 2020.	S
57	Yu, Bo *et al.* Low dose of hydroxychloroquine reduces fatality of critically ill patients with COVID-19 (vol 84, pg 913, 2020). 2020.	S

#	Study	Reason
58	Yu, bo *et al.* Beneficial effects exerted by hydroxychloroquine in treating COVID-19 patients via protecting multiple organs. Science China Life Sciences, v. 64, n. 2, p. 330-333, 2021.	S
59	Ader, florence. Protocol for the DisCoVeRy trial: multicentre, adaptive, randomized trial of the safety and efficacy of treatments for COVID-19 in hospitalised adults. BMJ open, v. 10, n. 9, p. e041437, 2020.	S
60	Göpel, Siri *et al.* Test and treat COVID 65 plus-Hydroxychloroquine versus placebo in early ambulatory diagnosis and treatment of older patients with COVID19: A structured summary of a study protocol for a randomized controlled trial. Trials, v. 21, n. 1, p. 1-2, 2020.	S
61	Akram, javed *et al.* Pakistan Randomized and Observational Trial to Evaluate Coronavirus Treatment (PROTECT) of Hydroxychloroquine, Oseltamivir and Azithromycin to treat newly diagnosed patients with COVID-19 infection who have no comorbidities like diabetes mellitus: A structured summary of a study protocol for a randomized controlled trial. Trials, v. 21, n. 1, p. 1-3, 2020.	S
62	Casey, Jonathan D. *et al.* Rationale and design of ORCHID: a randomized placebo-controlled clinical trial of hydroxychloroquine for adults hospitalized with COVID-19. Annals of the American Thoracic Society, v. 17, n. 9, p. 1144-1153, 2020.	S
63	Duška, František *et al.* Azithromycin added to hydroxychloroquine for patients admitted to intensive care due to coronavirus disease 2019 (COVID-19)—protocol of randomized controlled trial AZIQUINE-ICU. Trials, v. 21, n. 1, p. 1-11, 2020.	S
64	Duvignaud, Alexandre *et al.* Home Treatment of Older People with Symptomatic SARS-CoV-2 Infection (COVID-19): A structured Summary of a Study Protocol for a Multi-Arm Multi-Stage (MAMS) Randomized Trial to Evaluate the Efficacy and Tolerability of Several Experimental Treatments to Reduce the Risk of Hospitalisation or Death in outpatients aged 65 years or older (COVERAGE trial). Trials, v. 21, n. 1, p. 1-3, 2020.	S
65	Feeney, eoin *et al.* The COVIRL-001 Trial: A multicentre, prospective, randomized trial comparing standard of care (SOC) alone, SOC plus hydroxychloroquine monotherapy or SOC plus a combination of hydroxychloroquine and azithromycin in the treatment of non-critical, SARS-CoV-2 PCR-positive population not requiring immediate resuscitation or ventilation but who have evidence of clinical decline: A structured summary of a study protocol for a randomized controlled trial. Trials, v. 21, n. 1, p. 1-3, 2020.	S
66	Gautret, Philippe; VAN THUAN HOANG, Jean-Christophe Lagier; RAOULT, Didier. Effect of hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial, an update with an intention-to-treat analysis and clinical outcomes. International journal of antimicrobial agents, v. 57, n. 1, p. 106239, 2021.	S
67	Lofgren, sarah m. *et al.* Safety of hydroxychloroquine among outpatient clinical trial participants for COVID-19. In: Open forum infectious diseases. US: Oxford University Press, 2020. p. ofaa500.	P
68	Mitjà, oriol *et al.* A cluster-randomized trial of hydroxychloroquine for prevention of Covid-19. New England Journal of Medicine, 2020.	P
69	Nanni, Oriana *et al.* PROTECT Trial: A cluster-randomized study with hydroxychloroquine versus observational support for prevention or early-phase treatment of Coronavirus disease (COVID-19): A structured summary of a study protocol for a randomized controlled trial. Trials, v. 21, n. 1, p. 1-4, 2020.	P
70	Pirjani, Reihaneh *et al.* Effect of hydroxychloroquine on prevention of COVID-19 virus infection among healthcare professionals: a structured summary of a study protocol for a randomized controlled trial. Trials, v. 21, n. 1, p. 1-2, 2020.	P
71	Sivapalan, pradeesh *et al.* Proactive prophylaxis with azithromycin and hydroxychloroquine in hospitalised patients with COVID-19 (ProPAC-COVID): a structured summary of a study protocol for a randomized controlled trial. Trials, v. 21, n. 1, p. 1-4, 2020.	S
72	Vainio, Petri J. *et al.* Hydroxychloroquine in the treatment of adult patients with Covid-19 infection in a primary care setting (LIBERTY): A structured summary of a study protocol for a randomized controlled trial. Trials, v. 22, n. 1, p. 1-3, 2021.	S
73	Weehuizen, jesper m.; HOEPELMAN, Andy IM. An open-label cluster-randomized controlled trial of chloroquine, hydroxychloroquine or only supportive care in patients admitted with moderate to severe COVID-19 (ARCHAIC)—Protocol publication. 2020.	S

Appendix D. List of eligible RCTs without results.

#	Study	Note
1	Pilot trial on early treatment with hydroxychloroquine in patients with CSR	Protocol with no results
2	ChiCTR2000029939. A Single-blind, Randomized, Controlled Clinical Trial for Chloroquine Phosphate in the treatment of Novel Coronavirus Pneumonia 2019 (COVID-19) - *Full Text View - chictr.org.cn* (n.d.). Retrieved October 28, 2020, from http://www.chictr.org.cn/showproj.aspx?proj=49612	Protocol with no results
3	ChiCTR2000029559. Therapeutic effect of hydroxychloroquine on novel coronavirus pneumonia (COVID-19) - *Full Text View - chictr.org.cn* (n.d.). Retrieved October 28, 2020, from http://www.chictr.org.cn/showproj.aspx?proj=48880	Protocol with no results
4	ChiCTR2000029988. Clinical Study of Chloroquine Phosphate in the Treatment of Severe Novel Coronavirus Pneumonia (COVID-19) - *Full Text View - chictr.org.cn* (n.d.). Retrieved October 28, 2020, from http://www.chictr.org.cn/showproj.aspx?proj=49218	Protocol with no results
5	ChiCTR2000030718. Randomized controlled trial for Chloroquine Phosphate in the Treatment of novel coronavirus pneumonia (COVID-19) - *Full Text View - chictr.org.cn* (n.d.). Retrieved October 28, 2020, from http://www.chictr.org.cn/showproj.aspx?proj=50843	Protocol with no results
6	ACTRN12620000417987. Chloroquine Chemoprophylaxis Countermeasure against COVID-19 - *Full Text View - anzctr.org.au*. (n.d.). Retrieved October 29, 2020, from https://anzctr.org.au/ACTRN12620000417987.aspx	Protocol with no results
7	ISRCTN83971151. Public health emergency SOLIDARITY trial of treatments for COVID-19 infection in hospitalized patients. - *Full Text View - ISRCTN registry* (n.d.). Retrieved October 29, 2020, from https://doi.org/10.1186/ISRCTN83971151	Protocol with no results
8	2020-001224-33. Systematic study of the medicine hydroxychloroquine against placebo for the treatment of adult patients with acute coronavirus disease 2019 – COVID-19. - *Full Text View - ClinicalTrialsRegister.eu* (n.d.). Retrieved November 2, 2020, from https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001224-33	Protocol with no results
9	ChiCTR2000031204.A multicenter, single-blind, randomized controlled clinical trial for chloroquine phosphate in the treatment of novel coronavirus pneumonia (COVID-19). - *Full Text View - chictr.org.cn* (n.d.). Retrieved October 28, 2020, from http://www.chictr.org.cn/showproj.aspx?proj=49420	Protocol with no results
10	2020-001565-37. Prevention of novel Coronavirus infection with hydroxychloroquine. - *Full Text View - ClinicalTrialsRegister.eu* (n.d.). Retrieved October 28, 2020, from https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001565-37	Protocol with no results
11	2020-001188-96. Chemoprophylaxis of SARS-CoV-2 infection (COVID-19) in exposed healthcare workers: a randomized double-blind placebo-controlled clinical trial - *Full Text View - ClinicalTrialsRegister.eu* (n.d.). Retrieved November 2, 2020, from https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001188-96	Protocol with no results
12	2020-001421-31. Clinical trial for evaluation of efficacy and safety of hydroxychloroquine chemoprophylaxis against SARS-CoV-2 (COVID-19) infection in healthcare professionals - *Full Text View - ClinicalTrialsRegister.eu* (n.d.). Retrieved October 29, 2020, from https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001421-31	Protocol with no results
13	NCT04351724.Austrian Coronavirus Adaptive Clinical Trial (COVID-19) - *Full Text View - ClinicalTrials.gov* (n.d.). Retrieved October 29, 2020, from https://clinicaltrials.gov/ct2/show/NCT04351724	Protocol with no results
14	NCT04353037. PATCH 2&3: Prevention & Treatment of COVID-19 (Severe Acute Respiratory Syndrome Coronavirus 2) With Hydroxychloroquine - *Full Text View - ClinicalTrials.gov* (n.d.). Retrieved October 29, 2020, from https://clinicaltrials.gov/ct2/show/NCT04353037	Protocol with no results
15	2020-001331-26. Preventative Drug Treatment for COVID-19 Infectious Disease - *Full Text View - ClinicalTrialsRegister.eu* (n.d.). Retrieved October 29, 2020, from https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001331-26	Protocol with no results
16	RBR-3cbs3w. Evaluation of Hydroxychloroquine for prevention of hospitalization and respiratory complications in patients with confirmed diagnosis or suspected infection by (COVID-19) - *Full Text View - ensaiosclinicos.gov.br* (n.d.). Retrieved October 28, 2020, from http://www.ensaiosclinicos.gov.br/rg/RBR-3cbs3w/	Protocol with no results
17	IRCT20190122042450N4. The effect of hydroxychloroquine to prevent coronavirus disease - *Full Text View - irct.ir* (n.d.). Retrieved October 28, 2020, from https://en.irct.ir/trial/47090	Protocol with no results
18	IRCT20130917014693N10. Evaluation the effects of Hydroxychloroquine administration for COVID-19 prophylaxis - *Full Text View - irct.ir* (n.d.). Retrieved October 29, 2020, from https://en.irct.ir/trial/46849	Protocol with no results
19	IRCT20120826010664N6.Effect of hydroxychloroquine on prevention of covid-19 virus - *Full Text View - irct.ir* (n.d.). Retrieved October 29, 2020, from https://en.irct.ir/trial/46603	Protocol with no results
20	ISRCTN14326006. Does taking hydroxychloroquine before and during exposure to patients protect frontline healthcare workers from coronavirus? - *Full Text View - ISRCTN registry* (n.d.). Retrieved November 2, 2020, from https://doi.org/10.1186/ISRCTN14326006	Protocol with no results
21	ACTRN12620000445976.To compare the effectiveness of two drugs (hydroxychloroquine and lopinavir/ritonavir alone or combined in treating hospitalized patients with confirmed COVID-19 compared to standard of care - *Full Text View - anzctr.org.au*. (n.d.). Retrieved October 29, 2020, from https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12620000445976	Protocol with no results
22	NCT04370015. Hydroxychloroquine Chemoprophylaxis for COVID-19 Infection in High-risk Healthcare Workers: Randomized Control Trial - *Full Text View - ClinicalTrials.gov* (n.d.). Retrieved October 29, 2020, from https://clinicaltrials.gov/ct2/show/NCT04370015	Protocol with no results
23	2020-001366-11. An international randomized trial of additional treatments for COVID-19 in hospitalized patients who are all receiving the local standard of care - *Full Text View - ClinicalTrialsRegister.eu* (n.d.). Retrieved October 29, 2020, from https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001366-11	Protocol with no results
24	2020-001440-26. Study for the prevention of COVID-19 infection in healthcare personnel - *Full Text View - ClinicalTrialsRegister.eu* (n.d.). Retrieved October 29, 2020, from https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001440-26	Protocol with no results
25	ACTRN12620000501943. COVID-19 prophylaxis with hydroxychloroquine in Front-line Health and Allied-Health Care Workers: the COVID-SHIELD Trial - *Full Text View - anzctr.org.au*. (n.d.). Retrieved October 29, 2020, from https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12620000501943	Protocol with no results

#	Study	Note
26	ChiCTR2000031174. Effectiveness and safety of hydroxychloroquine sulfate in the preventive treatment of novel coronavirus pneumonia (COVID-19) - *Full Text View - chictr.org.cn* (n.d.). Retrieved October 29, 2020, from http://www.chictr.org.cn/showproj.aspx?proj=51437	Protocol with no results
27	ChiCTR2000032487.Study for using sulfate in the prevention and control of novel coronavirus pneumonia (COVID-19) in high and low prevalence communities - *Full Text View - chictr.org.cn* (n.d.). Retrieved October 29, 2020, from http://www.chictr.org.cn/showproj.aspx?proj=52394	Protocol with no results
28	2020-001704-42. Controlled and randomized trial to assess the safety and efficacy of hydroxychloroquine chemoprophylaxis in SARS CoV2 infection in hospital healthcare personnel (Sanitarios sin COVID-19) - *Full Text View - ClinicalTrialsRegister.eu* (n.d.). Retrieved October 29, 2020, from https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001704-42/ES	Protocol with no results
29	NCT04438837. Hydroxychloroquine Post-Exposure Prophylaxis for Coronavirus Disease (COVID-19) Among Health-Care Workers: A Randomized-Controlled Trial - *Full Text View - ClinicalTrials.gov* (n.d.). Retrieved October 29, 2020, from https://clinicaltrials.gov/ct2/show/NCT04438837	Protocol with no results
30	2020-001501-24. PROTECT: A randomized study with Hydroxychloroquine versus observational support for prevention or early phase treatment of Coronavirus disease (COVID-19) - *Full Text View - ClinicalTrialsRegister.eu* (n.d.). Retrieved October 29, 2020, from https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001501-24	Protocol with no results
31	2020-001441-39. Chloroquine/ hydroxychloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting; a randomized, placebo-controlled prophylaxis study (COPCOV) - *Full Text View - ClinicalTrialsRegister.eu* (n.d.). Retrieved November 02, 2020, from https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001441-39	Protocol with no results
32	2020-001987-28. PRECOV: a randomized controlled clinical trial on the effects of hydroxychloroquine in the prevention of COVID-19 in healthcare workers at risk - *Full Text View - ClinicalTrialsRegister.eu* (n.d.). Retrieved October 29, 2020, from https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001987-28	Protocol with no results
33	IRCT20200513047426N1 The prophylactic effect of oral hydroxy-chloroquine in close contacts of COVID-19 patients - *Full Text View - irct.ir* (n.d.). Retrieved October 29, 2020, from https://en.irct.ir/trial/48236	Protocol with no results
34	2020-001558-23. Hydroxychloroquine sulfate early administration in symptomatic out of hospital COVID-19 positive patients. Hydro-Stop-COVID19 Trial - *Full Text View - ClinicalTrialsRegister.eu* (n.d.). Retrieved October 29, 2020, from https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001558-23	Protocol with no results
35	ISRCTN10207947. Study of chloroquine/hydroxychloroquine and coronavirus disease (COVID-19) in the healthcare setting - *Full Text View - ISRCTN registry* (n.d.). Retrieved October 29, 2020, from https://doi.org/10.1186/ISRCTN10207947	Protocol with no results
36	CTRI / 2020/04/024479.Study of the effect of Chloroquine in addition to standard therapy in COVID-19 patients - *Full Text View - ctri.nic.in* (n.d.). Retrieved October 29, 2020, from http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=42713	Protocol with no results
37	PACTR202004801273802 Lagos COVID-19 Chloroquine Treatment Trial (LACCTT) - *Full Text View - pactr.samrc.ac.za* (n.d.). Retrieved October 29, 2020, from https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=10928	Protocol with no results
38	Cuadrado-Lavín, A., Olmos, J.M., Cifrian, J.M. *et al.* Controlled, double-blind, randomized trial to assess the efficacy and safety of hydroxychloroquine chemoprophylaxis in SARS CoV2 infection in healthcare personnel in the hospital setting: A structured summary of a study protocol for a randomized controlled trial. *Trials* 21, 472 (2020). https://doi.org/10.1186/s13063-020-04400-4	Protocol with no results
39	Denholm JT, Davis J, Paterson D, *et al.*; ASCOT Investigator Group. The Australasian COVID-19 Trial (ASCOT) to assess clinical outcomes in hospitalised patients with SARS-CoV-2 infection (COVID-19) treated with lopinavir/ritonavir and/or hydroxychloroquine compared to standard of care: A structured summary of a study protocol for a randomized controlled trial. Trials. 2020 Jul 14;21(1):646. doi: 10.1186/s13063-020-04576-9. PMID: 32665040; PMCID: PMC7359440.	Protocol with no results
40	Duška, František, *et al.* "Azithromycin added to hydroxychloroquine for patients admitted to intensive care due to coronavirus disease 2019 (COVID-19)—protocol of randomized controlled trial AZIQUINE-ICU." *Trials* 21.1 (2020): 1-11. https://doi.org/10.1186/s13063-020-04566-x	Protocol with no results
41	Feeney, E., Wallace, D., Cotter, A., Tinago, W., McCarthy, C., Keane, D., ... & Mallon, P. (2020). The COVIRL-001 Trial: A multicentre, prospective, randomized trial comparing standard of care (SOC) alone, SOC plus hydroxychloroquine monotherapy or SOC plus a combination of hydroxychloroquine and azithromycin in the treatment of non-critical, SARS-CoV-2 PCR-positive population not requiring immediate resuscitation or ventilation but who have evidence of clinical decline: A structured summary of a study protocol for a randomized controlled trial. *Trials*, *21*(1), 1-3. https://doi.org/10.1186/s13063-020-04407-x	Protocol with no results
42	Grau-Pujol, B., Camprubí, D., Marti-Soler, H. *et al.* Pre-exposure prophylaxis with hydroxychloroquine for high-risk healthcare workers during the COVID-19 pandemic: A structured summary of a study protocol for a multicentre, double-blind randomized controlled trial. *Trials* 21, 688 (2020). https://doi.org/10.1186/s13063-020-04621-7	Protocol with no results
43	*NCT04318444 - Hydroxychloroquine Post Exposure Prophylaxis for Coronavirus Disease (COVID-19)* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04318444	Recruiting in April 2020
44	*NCT04437693 - Post Exposure Prophylaxis in Healthcare Workers Exposed to COVID-19 Patients* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04437693	Still not recruiting in August 2020
45	*NCT04328272 - Effectiveness of Hydroxychloroquine in Covid-19 Patients* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04328272	Still not recruiting in April 2020
46	*NCT04318015 - Hydroxychloroquine Chemoprophylaxis in Healthcare Personnel in Contact With COVID-19 Patients (PHYDRA Trial)* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04318015	Recruiting in April 2020
47	*NCT04352933 - PROLIFIC ChemoprophylaxisTrial (COVID-19)* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04352933	Recruiting in May 2020
48	*NCT04363450 - Hydroxychloroquine as Prophylaxis for COVID-19 in Healthcare Workers (HCQPreP)* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04363450	Recruiting in September 2020
49	*NCT04371523 - Hydroxychloroquine to Prevent COVID-19 Disease Amongst Healthcare Workers* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04371523	Still not recruiting in May 2020

#	Study	Note
50	*NCT04385264 - #StayHome: Early Hydroxychloroquine to Reduce Secondary Hospitalization and Household Transmission in COVID-19* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04385264	Still not recruiting in May 2020
51	*NCT04466540 - Randomized Placebo-controlled Trial of Hydroxychloroquine in Outpatient Cases With Coronavirus Disease 2019 (COVID-19)* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04466540	Recruiting in November 2020
52	*NCT04342169 - University of Utah COVID-19 Hydrochloroquine Trial* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04342169	Recruiting in November 2020
53	*NCT04328961 - Hydroxychloroquine for COVID-19 Post-exposure Prophylaxis (PEP)* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04328961	Complete with no result in October 2020
54	*NCT04342221 - Hydroxychloroquine for COVID-19* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04342221	Recruiting in November 2020
55	*NCT04420247 - Efficacy of Chloroquine or Hydroxychloroquine in Treating Pneumonia Caused by SARS-Cov-2 - COVID-19* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04420247	Complete in October 2020 but has not posted results yet
56	*NCT04339816 - Azithromycin Added to Hydrochloroquine in Patients Admitted to Intensive Care With COVID-19: Randomized Controlled Trial* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04339816	Interrupted in November 2020
57	*NCT04352946 - HEalth Care Worker pROphylaxis Against COVID-19: The HERO Trial* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04352946	Still not recruiting in April 2020
58	*NCT04351516 - Test and Treat COVID 65plus+* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04351516	Interrupted in January 2021
59	*NCT04334148 - Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04334148	Complete with no result in February 2021
60	*NCT04397328 - COVID-19 PEP- High-risk Individuals in Long-term and Specialized Care - Canada* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04397328	Still not recruiting in May 2020
61	*NCT04372017 - Hydroxychloroquine as Post-Exposure Prophylaxis Against COVID-19 Infection* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04372017	Active in June 2020
62	*NCT04394442 - Hydroxychloroquine in COVID-19 Patients* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04394442	Recruiting in May 2020
63	*NCT04345692 - A Randomized Controlled Clinical Trial: Hydroxychloroquine for the Treatment of COVID-19 in Hospitalized Patients* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04345692	Interrupted in November 2020
64	*NCT04364815 - The University of the Philippines Hydroxychloroquine PEP Against COVID-19 Trial* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04364815	Interrupted in November 2020
65	*NCT04344444 - Treatment in Patients With Suspected or Confirmed COVID-19 With Early Moderate or Severe Disease* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04344444	Active in August 2020
66	*NCT04359537 - Efficacy of Various Doses of Hydroxychloroquine in Pre-Exposure Prophylaxis for COVID 19* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04359537	Recruiting in May 2020
67	*NCT04377646 - A Study of Hydroxychloroquine and Zinc in the Prevention of COVID-19 Infection in Military Healthcare Workers* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04377646	Still not recruiting in May 2020
68	*NCT04330144 - Hydroxychloroquine as Post Exposure Prophylaxis for SARS-CoV-2(HOPE Trial)* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04330144	Still not recruiting in April 2020
69	*NCT04372082 - Hydroxychloroquine or Diltiazem-Niclosamide for the Treatment of COVID-19* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04372082	Still not recruiting in May 2020
70	*NCT04466280 - Efficacy and Safety of Mucoadhesive Sustained Release, Mucodentol, in Comparison With Hydroxychloroquine to Prevent COVID-19* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04466280	Recruiting in July 2020
71	*NCT04340544 - Hydroxychloroquine for the Treatment of Mild COVID-19 Disease* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04340544	Interrupted in November 2020
72	*NCT04349592 - Hydroxychloroquine With or Without Azithromycin for Virologic Cure of COVID-19* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04349592	Complete with no results in February 2021
73	*NCT04414241 - Hydroxychloroquine to Prevent SARS-CoV-2 Infection* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04414241	Still not recruiting in June 2020
74	*NCT04346329 - Immune Monitoring of Prophylactic Effect of Hydroxychloroquine in Healthcare Providers Highly Exposed to COVID-19* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04346329	Still not recruiting in April 2020
75	*NCT04303507 - Chloroquine/ Hydroxychloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04303507	Recruiting in October 2020
76	*NCT04349371 - Saved From COVID-19* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04349371	Interrupted in February 2021
77	*NCT04328493 - The Vietnam Chloroquine Treatment on COVID-19* - 2020, from https://clinicaltrials.gov/ct2/show/NCT04328493	Recruiting in May 2020
78	Niriella, M.A., Ediriweera, D.S., De Silva, A.P. *et al.* Hydroxychloroquine for post-exposure prophylaxis of COVID-19 among naval personnel in Sri Lanka: study protocol for a randomized, controlled trial. *Trials* 21, 748 (2020). https://doi.org/10.1186/s13063-020-04659-7	Protocol with no result
79	TirupakuzhiVijayaraghavan, B.K., Jha, V., Rajbhandari, D. *et al.* Hydroxychloroquine plus personal protective equipment versus standard personal protective equipment alone for the prevention of COVID-19 infections among frontline healthcare workers: the Hydroxychloroquine Prophylaxis Evaluation(HOPE) trial: A structured summary of a study protocol for a randomized controlled trial. *Trials* 21, 754 (2020). https://doi.org/10.1186/s13063-020-04679-3	Protocol summary

Appendix E. List of RCTs included

#	Study
1	Abd-Elsalam, S., *et al.* Hydroxychloroquine in the Treatment of COVID-19: A Multicenter Randomized Controlled Study. The American journal of tropical medicine and hygiene, v.103, n. 4, p.1635–1639, 2020. DOI: https://doi.org/10.4269/ajtmh.20-0873
2	Cavalcanti A. B., *et al.* Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med, 2020. DOI: doi:10.1056/nejmoa2019014.
3	Chen, Zhaowei *et al.* Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv 2020.03.22.20040758; doi: https://doi.org/10.1101/2020.03.22.20040758
4	Chen, cheng-pin *et al.* A Multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate Coronavirus disease 2019 (COVID-19). medRxiv 2020.07.08.20148841; doi: https://doi.org/10.1101/2020.07.08.20148841
5	Chen, Lan *et al.* Efficacy and safety of chloroquine or hydroxychloroquine in moderate type of COVID-19: a prospective open-label randomized controlled study. Clinical and Translational Science, 2020. https://doi.org/10.1101/2020.06.19.20136093
6	Chen, jung *et al.* A pilot studyof hydroxychloroquine in treatment of patients with moderate COVID-19. Journal of Zhejiang University, 49(2), p. 215-219, 2019
7	The RECOVERY Collaborative Group. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med, v. 383, p. 2030-2040, 2020. DOI: 10.1056/NEJMoa2022926. Horby *et al.* Effect of hydroxychloroquine in hospitalized patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial.medRxiv; 2020 [cited 2021 Feb 24]. p. 2020.07.15.20151852. Available from: https://doi.org/10.1101/2020.07.15.20151852.
8	Kamran, Mehmood *et al.* Clearing the fog: Is Hydroxychloroquine effective in reducing Corona virus disease-2019 progression: A randomized controlled trial. medRxiv 2020.07.30.20165365; doi: https://doi.org/10.1101/2020.07.30.20165365
9	Mitjà, oriol *et al.* Hydroxychloroquine for early treatment of adults with mild Covid-19: a randomized-controlled trial. Clinical Infectious Diseases, 2020. Doi: 10.1093/cid/ciaa1009
10	Skipper, Caleb P. *et al.* Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. Annals of internal medicine, 2020. doi: 10.7326/M20-4207
11	Tang, wei *et al.* Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. MedRxiv, 2020. doi: https://doi.org/10.1101/2020.04.10.20060558
12	Lyngbakken *et al.* A pragmatic randomized controlled trial reports lack of efficacy of hydroxychloroquine on coronavirus disease 2019 viral kinetics. Nature Communications, v. 11, n.5284, 2020.
13	Omrani *et al.* Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe Covid-19. EClinicalMedicine, v. 29-30, 2020.
14	Self *et al.* Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial. JAMA, v. 324, n. 21, p. 2165-2176, 2020. DOI: 10.1001/jama.2020.22240.
15	Ulrich *et al.* Treating COVID-19 with hydroxychloroquine (TEACH): a multicenter, double-blind, randomized controlled trial in hospitalized patients. Open Forum Infect Dis., v. 7, n. 10, 2020.
16	WHO Solidarity Trial Consortium. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. The New England Journal of Medicine, v. 384, n. 6, 2021. DOI: 10.1056/NEJMoa2023184. WHO Solidarity Trial Consortium. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. The New England Journal of Medicine, 2020. 10.1056/NEJMoa2023184.

Appendix F. Characteristics of included studies.

Study	**Abd-Elsalam *et al.* 2020**
General characteristics	Objective: Assessing HCQ safety and efficacy added to the SOC compared to the SOC for patients with COVID-19. Design: RCT Population: Patients with confirmed or suspected COVID-19 Age: mean (SD) – 40.72 (±19.32) Sample size: 194 [HCQ + SOC (n=97) vs. SOC (n=97)] Interventions: HCQ + SOC vs. SOC Follow-up: 28 days Place: Egypt Registry: NCT04353336
Efficacy	There was no significant difference between groups in terms of the number of patients requiring mechanical ventilation [HCQ+SOC (4 patients; 4.1%) vs. SOC (5 patients; 5.2%), p-value=0.75], number of patients admitted to the ICU [HCQ+SOC (11 patients; 11.3%) vs. SOC (13 patients; 13.4%), p-value=0.83)], time until clinical improvement [HCQ+SOC (mean±SD=9±2 days) vs. SOC (mean±SD=10±3 days), p-value=0.80], time to hospital discharge [HCQ+SOC (mean±SD=11±3 days) vs. SOC (mean±SD=11±2 days), p-value=0.52], mortality in 28 days [HCQ+SOC (6 patients; 6.2%) vs. SOC (5 patients; 5.2%), p-value=0.76], and complete recovery in 28 days [52 cases (53.6%) in the HCQ + SOC group and 33 (34.0%) in the group SOC alone, p-value=0.06]. Mortality was not associated with treatment, but was significantly associated with age, alanine aminotransferase, serum creatinine, serum ferritin, C-reactive protein, oxygen saturation, and the presence of diabetes mellitus.
Conclusion	HCQ was not effective as a treatment for COVID-19 patients.
Notes	
References	Abd-Elsalam, S., *et al.* Hydroxychloroquine in the Treatment of COVID-19: A Multicenter Randomized Controlled Study. The American journal of tropical medicine and hygiene, v.103, n. 4, p.1635–1639, 2020. DOI: https://doi.org/10.4269/ajtmh.20-0873

*HCQ=Hydroxychloroquine; RCT=Randomized Controlled Trial; SOC=Standard-of-care; SD=Standard deviation.

Study	**Cavalcanti *et al*, 2020**
General characteristics	Objective: Evaluating if HCQ alone or in association with Az is safe and effective for treating mild-to-moderate COVID-19 patients. Design: RCT Population: Hospitalized adult patients with suspected or confirmed COVID-19 infection. Age: ≥18 years old, mean±SD=50.3±14.6 Sample size: N=667 – 221 (HCQ+SOC) vs. 217 (HCQ+AZT+SOC) vs. 229 (SOC) Interventions: SOC vs. SOC + HCQ vs. SOC + HCQ + AZT Follow-up: 15 days Place: Brazil Registry: NCT04322123
Efficacy	Among confirmed Covid-19 patients, there were no significant differences between groups in the proportional chances of having a higher score on the seven-point ordinal scale in 15 days [HCQ+Az vs. SOC (OR=0.99; CI95%=0.57 to 1.73; p-value=1.00); HCQ vs. SOC (OR=1.21; CI95%=0.69 to 2.11; p-value=1.00); and HCQ+Az vs. HCQ (OR=0.82; CI95%=0.47 to 1.43; p-value=1.00). 11.0% of the patients in the HCQ+Az group, 7.5% in the HCQ group, and 6.9% in the SOC group received mechanical ventilation during the first 15 days. The mean±SD number of days without respiratory support was 11.1±4.9 in the HCQ+Az group, 11.2±4.9 in the HCQ group, and 11.1±4.9 in the SOC group. Five patients died in the HCQ+Az group, 7 in the HCQ group, and 6 in the SOC group. There were no significant differences between the groups regarding the secondary results of thromboembolic complications or acute kidney injury in 15 days, both in pre-specified analyzes and in post hoc analyzes that considered the competitive risk of death.
Safety	More adverse events were reported in patients who received HCQ+AZT (39.3%) or HCQ (33.7%) than those who received AZT (18.0%) or SOC (22.6%). Serious adverse events occurred in 2.1% in the HCQ + Az group, 1.0% in HCQ and 1.1% in the SOC group, and none in the Az group. The QTc interval prolongation was more common in patients receiving HCQ + Az or HCQ than patients in the SOC group.
Conclusion	HCQ did not improve efficacy outcomes and is associated with more adverse events than SOC.
Notes	Funded by EMS Pharma
References	Cavalcanti A. B., *et al.* Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med, 2020. DOI: doi:10.1056/nejmoa2019014.

*Az=Azithromycin; HCQ=Hydroxychloroquine; RCT=Randomized Controlled Trial; SOC=Standard-of-care; SD=Standard deviation.

Study	**Chen, Z *et al*. 2020**
General characteristics	Objective: Evaluating the efficacy of HCQ for COVID-19 treatment Design: RCT Population: Patients confirmed to have a COVID-19 infection. Age: ≥ 18 years old, mean±SD=44.7±15.3 years old Sample size: N=62 – 31 (HCQ) vs 31 (SOC) Interventions: SOC+HCQ vs. SOC Follow-up: 5 days Place: China Registry: ChiCTR2000029559
Efficacy	Compared to the control group, the body temperature recovery time and cough remission time were significantly reduced in the HCQ treatment group. Notably, a total of 4 of the 62 patients progressed to severe illness, all occurring in the control group that did not receive HCQ treatment.
Safety	For adverse effects, it should be noted that there were two patients with mild adverse reactions in the HCQ treatment group, one patient developed a rash, and one patient had a headache, but no severe side effects appeared in them.
Conclusion	Despite our small number of cases, HCQ+SOC was considered more effective than SOC to shorten clinical response time and control pneumonia.
Notes	Exclusion criteria for this study were patients with severe and critical illnesses, retinopathy and other retina diseases, conduction block and other arrhythmias, severe liver disease, severe renal failure, and who received an experimental treatment for COVID-19 30 days before the research. The follow-up time is too short, and there is a risk of selective reporting. The authors do not focus on outcomes.
References	CHEN, Zhaowei *et al.* Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv 2020.03.22.20040758; doi: https://doi.org/10.1101/2020.03.22.20040758

*HCQ=Hydroxychloroquine; RCT=Randomized Controlled Trial; SOC=Standard-of-care; SD=Standard deviation.

Study	**Chen, C *et al*. 2020**
General characteristics	Objective: Assessing the efficacy of HCQ against COVID-19. Design: RCT Population: Adult patients with confirmed mild-to-moderate COVID-19. Age: 22-68 years old (mean±SD=32.9±10.7). Sample size: N=33 – 21 (HCQ) vs. 12 (SOC) Interventions: HCQ/SOC vs. SOC Follow-up time: 14 days Place: Taiwan Registry: NCT04384380
Efficacy	This RCT revealed no significant difference between the treatment group and SOC at the primary endpoint to shorten the viral clearance interval. On the 14th day, 81.0% (17 people) from the HCQ group and 75.0% (9 people) from the SOC group had negative PCR results for COVID-19. The median time to negative rRT-PCR test was 5 days (95%CI=1–9 days) in the HCQ group and 10 days (95%CI=2–12) in the SoC group.
Safety	There was no mortality in the present study, and no serious adverse events were reported.
Conclusion	The study failed to demonstrate HCQ efficacy at shortening viral shedding in subjects with mild to moderate COVID-19 symptoms.
Notes	Participants who had severe illness and specific comorbidities were excluded from this study.
References	CHEN, Cheng-Pin *et al.* A Multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate Coronavirus disease 2019 (COVID-19). medRxiv 2020.07.08.20148841; doi: https://doi.org/10.1101/2020.07.08.20148841

*HCQ=Hydroxychloroquine; RCT=Randomized Controlled Trial; SOC=Standard-of-care; SD=Standard deviation.

Study	Chen, L *et al*.. 2020
General characteristics	Objective: Evaluating effects of chloroquine and hydroxychloroquine to treat COVID-19. Design: RCT Population: Adult patients with confirmed moderate COVID-19. Age: 18 to 75 years old; mean±SD=45.22±13.66 years (CQ) vs. 45.67±14.37 years (HCQ) vs. 51.33 ± 15.36 years (SOC) Sample size: N=48; 18 (CQ) vs. 18 (HCQ) vs. 12 (SOC) Interventions: CQ vs. HCQ vs. SOC Follow-up time: 28 days or until hospital discharge Place: China Registry: ChiCTR2000030054
Efficacy	Patients in the CQ group achieved clinical response faster than patients in the control group. This difference was not seen with HCQ. Compared to the SOC, CQ and HCQ groups achieved PCR negativity faster. There was also a modest decrease in time to discharge, coherent with the faster PCR negativity.
Safety	17/36 patients in the CQ/HCQ group presented adverse events compared to 2/14 patients in the control group. No severe adverse events were observed.
Conclusion	CQ and HCQ were associated with clinical benefits regarding time to achieve negative PCR results and clinical response.
Notes	Small sample. A low number of events. No outcomes were included. The follow-up was short this time horizon might not have caught some events. No deaths were seen.
References	CHEN, Lan *et al.* Efficacy and safety of chloroquine or hydroxychloroquine in moderate type of COVID-19: a prospective open-label randomized controlled study. Clinical and Translational Science, 2020. https://doi.org/10.1101/2020.06.19.20136093

*HCQ=Hydroxychloroquine; RCT=Randomized Controlled Trial; SOC=Standard-of-care; SD=Standard deviation.

Study	Chen, J *et al*. 2020
General characteristics	Objective: Evaluating the efficacy and safety of hydroxychloroquine for treating moderate COVID-19. Design: RCT Population: Treatment-naïve patients with confirmed moderate COVID-19 Age: NA Sample size: N=30; 15 (HCQ) vs. 15 (SOC) Interventions: HCQ vs. SOC Follow-up time: 7 days Place: China Registry: NCT04261517
Efficacy	The median duration from hospitalization to negative PCR was four days in the HCQ group and two days for SOC group (p-value>0.05). On day 7, swabs were negative in 13 cases in the HCQ group and 14 cases in the SOC group.
Safety	Four cases in the HCQ group and three cases in the SOC group had transient diarrhea and abnormal liver function (p-value>0.05).
Conclusion	No advantage for the HCQ group was observed in the study.
Notes	Small samples, number of events and follow-up.
References	CHEN, Jung *et al.* A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. Journal of Zhejiang University, 49(2), p. 215-219, 2019.

*HCQ=Hydroxychloroquine; RCT=Randomized Controlled Trial; SOC=Standard-of-care; SD=Standard deviation.

Study	RECOVERY
General characteristics	Objective: Evaluating the efficacy and safety of some drugs for COVID-19 treatment, including hydroxychloroquine. Design: RCT Population: Confirmed or suspected COVID-19 patients Age: 65.2±15.2 (HCQ) vs. 65.4±15.4 (SOC) Sample size: N=4674; 1561 (HCQ) vs. 3155 (SOC) Interventions: HCQ vs. SOC vs. Lopinavir-Ritonavir vs. Dexamethasone vs. Azithromycin vs. Tocilizumab vs. Convalescent plasma Follow-up time: 28 days Place: United Kingdom Registry: NCT04381936
Efficacy	Death within 28 days occurred in 421 patients (27.0%) in the hydroxychloroquine group and in 790 (25.0%) in the usual-care group (RR=1.09; CI95% 0.97 to 1.23; p-value=0.15). Patients allocated to the HCQ group were less likely to be discharged from the hospital alive within 28 days than those in the SOC group (59.6% vs. 62.9%; rate ratio, 0.90; CI95%, 0.83 to 0.98).
Safety	There was a slight excess of cardiac deaths (0.4%) but no difference in the incidence of new major cardiac arrhythmia among patients who received HCQ.
Conclusion	HCQ was not associated with reductions in 28-day mortality but was associated with an increased length of hospital stay and increased risk of progressing to invasive mechanical ventilation or death.
Notes	
References	The RECOVERY Collaborative Group. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med, v. 383, p. 2030-2040, 2020. DOI: 10.1056/NEJMoa2022926. Horby *et al.* Effect of hydroxychloroquine in hospitalized patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial. medRxiv; 2020 [cited 2021 Feb 24]. p. 2020.07.15.20151852. Available from: https://doi.org/10.1101/2020.07.15.20151852.

*HCQ=Hydroxychloroquine; RCT=Randomized Controlled Trial; SOC=Standard-of-care; SD=Standard deviation.

Study	**Kamran *et al.* 2020**
General characteristics	Objective: Analyzing the effectiveness of HCQ+SOC compared to SOC alone in reducing disease progression in mild COVID-19 patients. Design: RCT Population: Patients with confirmed mild COVID-19. Age: 18 to 50 years old; mean±SD=35.96±11.2. Sample size: 500 patients - 349 (HCQ) vs. 151 (SOC) Intervention: HCQ vs. SOC Follow-up: 14 days Place: Pakistan Registry: NCT04491994
Efficacy	Despite significantly showing early PCR negativity on day 7 [182 people (52.1%) in the HCQ group vs. 54 people (35.8%) in the SoC group], the results of PCR on day 14 are similar to those in the non-HCQ arm [244 people (69.9%) in the HCQ group vs. 110 people (72.9%) in the SOC group]. 240 people (68.8%) in the HCQ group and 106 people (70.1%) in the group SoC presented negative results in the PCR exam on days 7 and 14. Thirty-six patients (10.3%) from the HCQ group and 8 patients (5.3%) from the SoC group were negative for 7 days but were positive on day 14. The disease progressed 11 people (3.15%) in the intervention group and 5 people (3.3%) in the control group (p-value=0.94)
Safety	
Conclusion	Adding HCQ to supportive treatment in mild cases of COVID-19 is not significantly associated with preventing disease progression.
Notes	Most patients were healthy young people with comorbidities in only 7.6% of cases. 20.2% of patients were asymptomatic. In addition, a subset of patients who were PCR negative on day 7 became positive again on day 14. This observation may be due to false-negative PCR on day 7 or false-positive PCR on day 14.
References	KAMRAN, Mehmood *et al.* Clearing the fog: Is Hydroxychloroquine effective in reducing Corona virus disease-2019 progression: A randomized controlled trial. medRxiv 2020.07.30.20165365; doi: https://doi.org/10.1101/2020.07.30.20165365

*HCQ=Hydroxychloroquine; RCT=Randomized Controlled Trial; SOC=Standard-of-care; SD=Standard deviation.

Study	**Mitjà *et al.* 2020**
General characteristics	Objective: Evaluating the efficacy and safety of HCQ initiated early for treating outpatients with mild Covid-19. Design: RCT Population: Non-hospitalized adult patients with mild COVID-19 symptoms for less than five days before enrollment. Age: >18 years old; mean±SD=41.6±12.6 years old. Sample size: 293 – 136 (HCQ) vs 157 (SOC) Intervention: HCQ vs SOC Follow-up: 28 days Place: Spain Registry: NCT04304053
Efficacy	There was no significant difference in the mean viral load reduction, collected in the nasopharyngeal region between HCQ and SoC groups on days 3 (-1.41 Log10 copies/mL vs. -1.41 Log10 copies/mL, respectively) and 7 (–3.44 Log10 copies/mL vs. –3.37 Log10 copies/mL, respectively). The risk of hospitalization was similar in both groups (5.9% in the HCQ group vs. 7.1% in the SoC group), and the median time to end symptoms was 10 days in the HCQ group and 12 days in the control group.
Safety	8.7% of the control group and 72% of the HCQ group had at least one adverse event during follow-up. Fifty-seven patients (33.9%) in the intervention group had adverse events grade 3 or higher compared to one patient (0.5%) in the control group.
Conclusion	The study found no advantage of HCQ to treat patients with Covid-19 early stage. The use of the drug was associated with an increase in grade 3 or higher adverse events.
Notes	Efficacy was measured by varying the average viral load collected in the patient's nasopharyngeal region. Clinical assessments on day 7 were not originally scheduled, and therefore the number of patients tested for viral positivity was lower than day 3. Another factor is that the trial cannot be masked with a placebo, which may have affected the declared AE rate.
References	MITJÀ, Oriol *et al.* Hydroxychloroquine for early treatment of adults with mild Covid-19: a randomized-controlled trial. Clinical Infectious Diseases, 2020. Doi: 10.1093/cid/ciaa1009

*HCQ=Hydroxychloroquine; RCT=Randomized Controlled Trial; SOC=Standard-of-care; SD=Standard deviation.

Study	**Skipper *et al.* 2020**
General characteristics	Objective: Evaluating the HCQ effectiveness in non-hospitalized patients after the first symptoms of Covid-19. Design: RCT Population: Non-hospitalized adult patients with less than 4 days of symptoms and either a PCR test positive to COVID-19 or symptoms of COVID-19 after a high-risk exposure. Age: Median of 40 years old (IQR=32-50) Sample size: 491 (244 for HCQ vs. 247 for placebo) Interventions: HCQ vs. Placebo Follow-up: 14 days Place: USA and Canada Registry: NCT04308668
Efficacy	The HCQ group showed an average reduction of 2.6 points in the symptom severity scale compared to the average decrease of 2.33 in the placebo group. With only one death in each group, the incidence of hospitalization and deaths did not differ between the HCQ group and the placebo group (P = 0.29).
Safety	After 5 days in the HCQ group, adverse events were 43% and 22% in the placebo group.
Conclusion	The study showed no efficacy of hydroxychloroquine in patients with Covid-19 first symptoms. The intervention was associated with a higher adverse event probability.
Notes	People with confirmed Covid-19 or compatible symptoms were selected. Due to the low death and hospitalization rates, an assessment of symptom severity was added to the study using a 10-point visual analog scale.
References	SKIPPER, Caleb P. *et al.* Hydroxychloroquine in non-hospitalized adults with early COVID-19: a randomized trial. Annals of internal medicine, 2020. doi: 10.7326/M20-4207

*HCQ=Hydroxychloroquine; RCT=Randomized Controlled Trial; SOC=Standard-of-care; SD=Standard deviation.

Study	Tang *et al.* 2020
General characteristics	Objective Evaluating the HCQ efficacy and safety combined with SoC in adult patients with mild to moderate COVID-19 Design: RCT Population: Hospitalized adults with confirmed COVID-19 Age: mean±SD=46.1±14.7 Sample size: 150 – 75 (HCQ+SOC) vs. 75 (SOC) Interventions: HCQ + SOC vs. SOC Follow-up: 28 days (mean of 21 days in the SOC group and 20 days in the HCQ+SOC group) Place: China Registry: ChiCTR2000029868
Efficacy	The probability of negative conversion of Sars-CoV-2 was 85.4% (CI95%=73.8% to 93.8%) for the HCQ+SOC group and 81.3% (CI95% =71.2% to 89.6%) in the SOC group. The median time to negative test was 8 days in the HCQ+SOC group and 7 days in the SOC group. After 28 days, the symptom relief was 59.9% (CI95%=45.0% to 75.3%) in the HCQ+SOC group, with a median of 19 days and 66.6% (CI95% =39.5% to 90.9%) in the SOC group with a median of 21 days.
Safety	30% of the HCQ + SOC group had adverse events, against 8.8% of the SOC group.
Conclusion	HCQ was not considered more effective than SOC alone in patients mainly hospitalized with persistent mild to moderate COVID–19. Adverse events were higher in HCQ recipients than in HCQ non–recipients.
Notes	60% of patients (N=90) received concomitant medication before randomization, 52 (34.7%) of whom had antivirals. The trial was terminated early.
References	TANG, Wei *et al.* Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. MedRxiv, 2020. doi: https://doi.org/10.1101/2020.04.10.20060558

*HCQ=Hydroxychloroquine; RCT=Randomized Controlled Trial; SOC=Standard-of-care; SD=Standard deviation.

Study	NO COVID-19
General characteristics	Objective: Evaluating the HCQ efficacy and safety compared to SOC for COVID-19 treatment. Design: RCT Population: Adult patients with PCR confirmed COVID-19. Age: >18 years old; median=62 (IQR=50 to 73). Sample size: N=53; 27 (HCQ+SOC) vs. 26 (SOC) Interventions: HCQ+SOC vs. SOC Follow-up: 30 days Place: Norway Registry: NCT04332991
Efficacy	One patient died in each arm. There was no difference between groups regarding the reduction rate in SARS-CoV-2 viral load (reduction rate difference between the groups 0.11 [CI95% –0.21 to 0.43] log 10 RNA copies/mL/24h).
Safety	237 adverse events were reported [125 (HCQ) vs. 112 (SOC)]. Five patients were on HCQ, and 6 in the SOC group
Conclusion	The results suggest no significant antiviral effect of hydroxychloroquine in humans infected with SARS-CoV-2.
Notes	Tiny study. Focus on intermediate outcomes.
References	Lyngbakken *et al.* A pragmatic randomized controlled trial reports lack of efficacy of hydroxychloroquine on coronavirus disease 2019 viral kinetics. Nature Communications, v. 11, n.5284, 2020.

*HCQ=Hydroxychloroquine; RCT=Randomized Controlled Trial; SOC=Standard-of-care; SD=Standard deviation.

Study	Q-PROTECT
General characteristics	Objective: Assessing the HCQ±Az efficacy of HCQ±Az for treating non-severe COVID-19 patients. Design: RCT Population: Researchers planned to include a population consisting of PCR-positive COVID-19 males and females with mild or no symptoms, but, in practice, the Q-PROTECT sample was composed of young, expatriate males. Age: median=42 (IQR=38-48) for HCQ+Az vs. 40 (IQR=31-47) for HCQ vs. 41 (IQR=31-47) for Placebo Sample size: N=456; 152 (HCQ) vs. 152 (HCQ+Az) vs. 152 (Placebo) Interventions: HCQ vs. HCQ+Az vs. Placebo Follow-up: 14 days Place: Qatar Registry: NCT04332991
Efficacy	The study showed no difference between study groups regarding viral cure [HC+AZ (30/149) vs. HC (42/146) vs. placebo (45/143), p-value=0.072]. No deaths were observed.
Safety	No serious adverse event was observed.
Conclusion	HC±Az does not facilitate virologic cure in patients with mild or asymptomatic Covid-19.
Notes	Triple-blinded.
References	Omrani *et al.* Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe Covid-19. EClinicalMedicine, v. 29-30, 2020.

*HCQ=Hydroxychloroquine; RCT=Randomized Controlled Trial; SOC=Standard-of-care; SD=Standard deviation.

Study	ORCHID
General characteristics	Objective: Determining whether hydroxychloroquine is an effective treatment for COVID-19 hospitalized adults. Design: RCT Population: Adults (aged≥18years) who were hospitalized for less than 48 hours with laboratory-confirmed SARS-CoV-2 infection and symptoms of respiratory illness for less than 10 days were enrolled. Age: median=57 years old. Sample size: N=479; 242 (HCQ) vs. 237 (Placebo) Interventions: HCQ vs. Placebo Follow-up: 28 days Place: USA Registry: NCT04332991
Efficacy	No difference was observed in any of the 13 efficacy outcomes included. 25 out of 242 patients in the HCQ group and 25 out of 237 patients in the placebo group died at the 28-day follow-up.
Safety	14/242 patients in the HCQ group and 11/236 patients in the placebo group presented severe adverse events.
Conclusion	Among adults hospitalized with respiratory illness from COVID-19, the treatment with hydroxychloroquine, compared with placebo, did not significantly improve clinical status at day 14 or reduced mortality at day 28.
Notes	The trial was stopped at the fourth interim analysis for futility with a sample size of 479 patients. 13 outcomes were included. Blinded.
References	Self *et al.* Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial. JAMA, v. 324, n. 21, p. 2165-2176, 2020. DOI: 10.1001/jama.2020.22240.

*HCQ=Hydroxychloroquine; RCT=Randomized Controlled Trial; SOC=Standard-of-care; SD=Standard deviation.

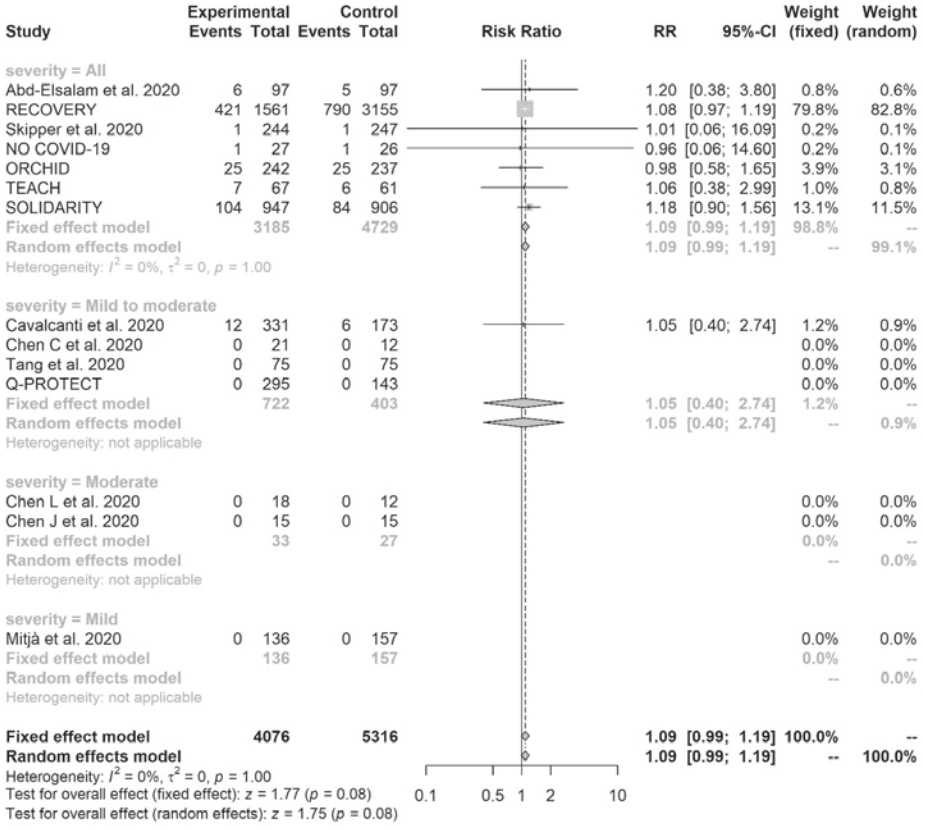
Study	TEACH
General characteristics	Objective: Determining the HCQ safety and efficacy for treating COVID-19 hospitalized patients. Design: RCT Population: Patients with a positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) Age: mean±SD=66.2±16.2; 66.5±16.4 (HCQ) vs. 65.8±16.0. Sample size: N=128; 67 (HCQ) vs. 61 (Placebo) Interventions: HCQ vs. Placebo Follow-up: 30 days. Place: USA Registry: NCT04332991
Efficacy	No statistical significance was observed between HCQ and placebo regarding severe disease progression at day 15 (p-value=0.350). There were no significant differences in COVID-19 clinical scores, number of oxygen-free days, SARS-CoV-2 clearance, or adverse events between HCQ and placebo. No significant difference was observed for mortality within 30 days (p-value=1).
Safety	No difference was observed regarding the number of patients with adverse events (38 vs. 36, p-value=0.933) or severe adverse events (9 vs. 8, p-value=1)
Conclusion	In COVID-19 hospitalized patients, our data suggest that HCQ does not prevent severe outcomes or improve clinical scores.
Notes	Double-blind.
References	Ulrich *et al.* Treating COVID-19 with hydroxychloroquine (TEACH): a multicenter, double-blind, randomized controlled trial in hospitalized patients. Open Forum Infect Dis., v. 7, n. 10, 2020.

*HCQ=Hydroxychloroquine; RCT=Randomized Controlled Trial; SOC=Standard-of-care; SD=Standard deviation.

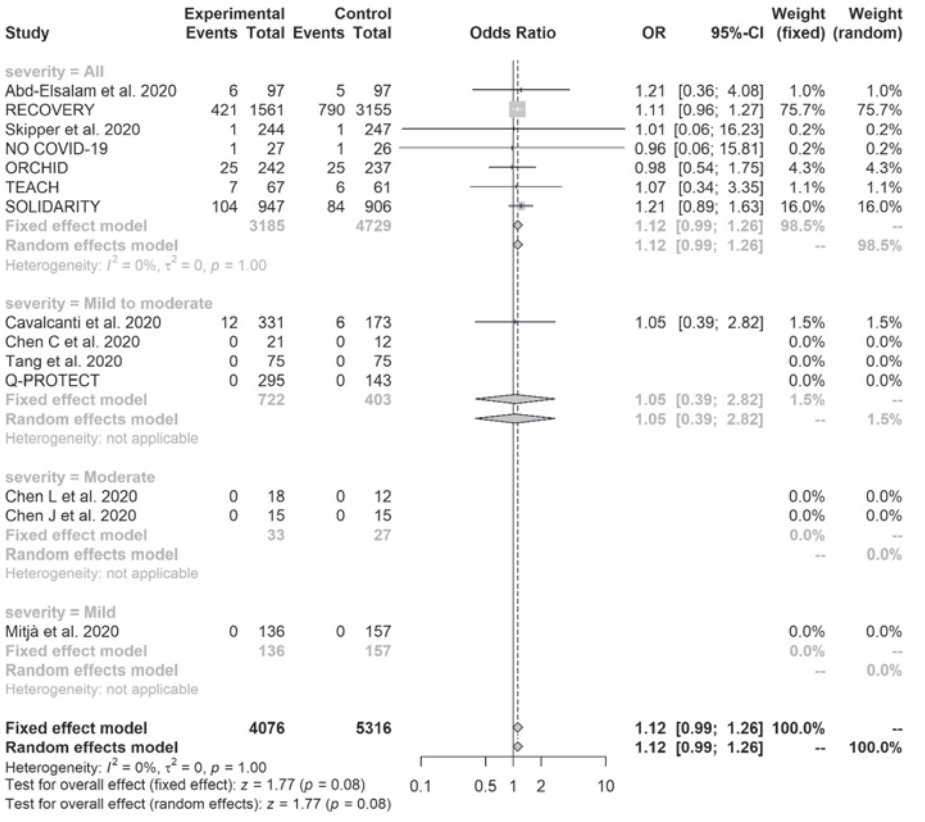
Study	SOLIDARITY
General characteristics	Objective: Evaluating effects of four drugs on in-hospital mortality of COVID-19 patients. Design: RCT Population: Patients were 18 years of age or older, hospitalized with Covid-19 diagnosis, not known to have received any trial drug, not expected to be transferred elsewhere within 72 hours, and, in the physician's view, had no contraindication to any trial drug. Age: 9120 patients (81%) were younger than 70 years of age. Sample size: N=11,330; 954 (HCQ+SOC) vs. 906 (SOC) Interventions: HCQ vs. remdesivir vs. lopinavir vs. interferon vs. no trial drug. Follow-up: 28 days. Place: 30 countries. Registry: NCT04332991
Efficacy	Death occurred in 104 of 947 patients receiving hydroxychloroquine and in 84 of 906 receiving placebo (RR=1.19; CI95%=0.89-1.59; p-value=0.23)
Safety	NA
Conclusion	No drug definitely has reduced mortality, overall or in any subgroup, or reduced initiation of ventilation or hospitalization duration.
Notes	NA
References	WHO Solidarity Trial Consortium. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. The New England Journal of Medicine, v. 384, n. 6, 2021. DOI: 10.1056/NEJMoa2023184.

*HCQ=Hydroxychloroquine; RCT=Randomized Controlled Trial; SOC=Standard-of-care; SD=Standard deviation.

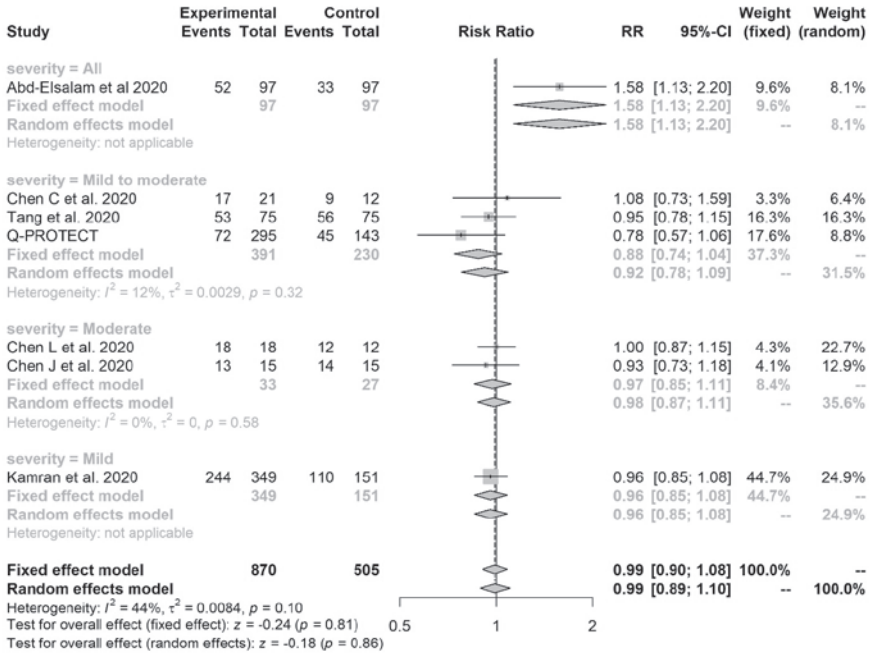
Appendix G. Sensitivity analysis method to aggregate data: mortality at the most extended follow-up using the Mantel–Haenszel method



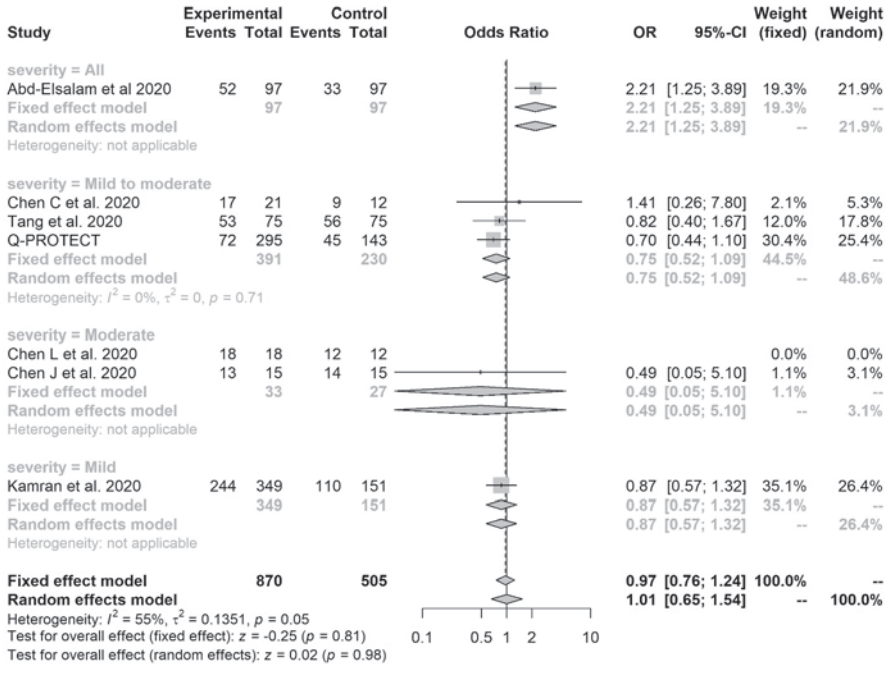
Appendix H. Sensitivity analysis method to aggregate data: mortality at the most extended follow-up using the Peto's method



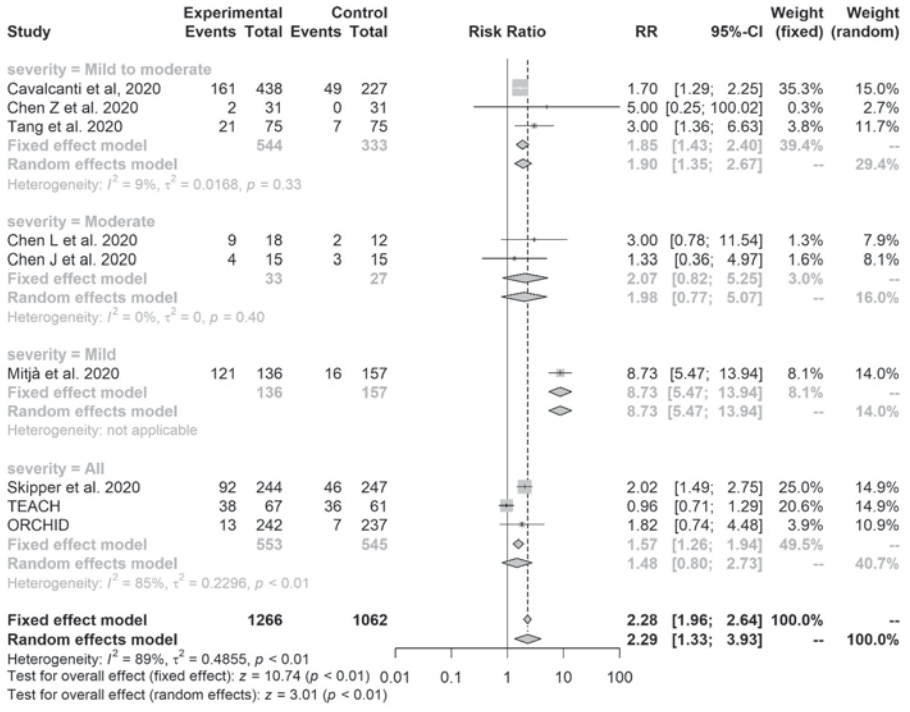
Appendix I. Sensitivity analysis method to aggregate data: cure at the most extended follow-up using the Mantel–Haenszel method



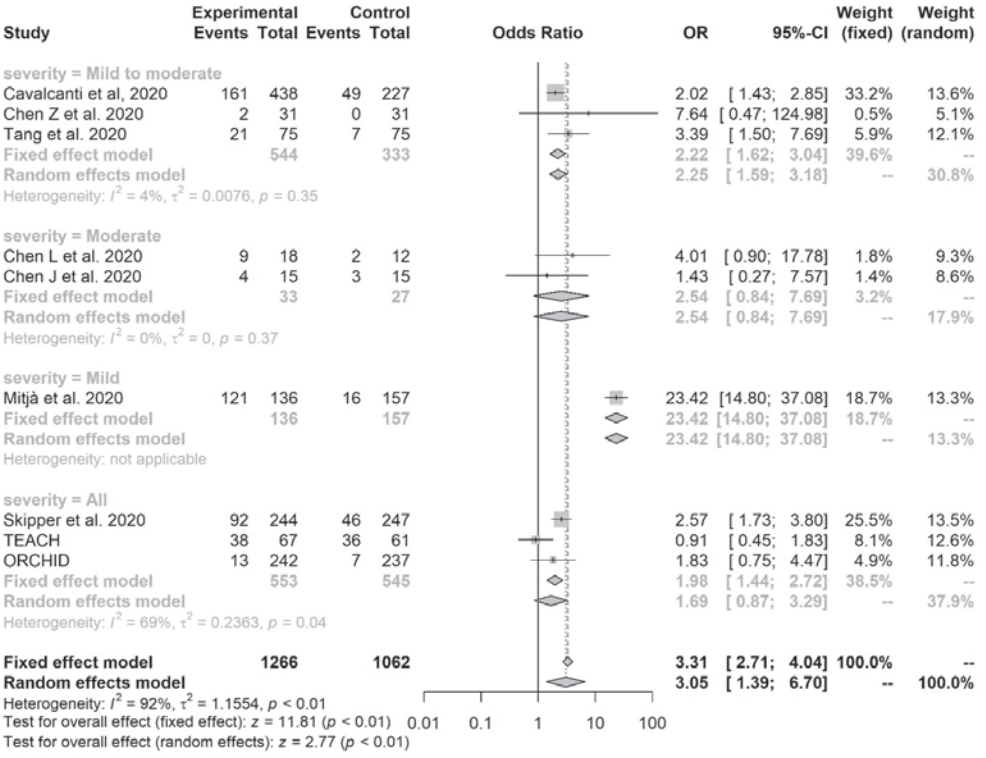
Appendix J. Sensitivity analysis method to aggregate data: cure at the most extended follow-up using the Peto's method



Appendix K. Sensitivity analysis method to aggregate data: adverse events using the Mantel–Haenszel method



Appendix L. Sensitivity analysis method to aggregate data: adverse events using the Peto's method



Appendix M. Meta-regression for adverse event outcomes

Mixed-Effects Model (k = 9; tau^2 estimator: DL)

tau^2 (estimated amount of residual heterogeneity): 0.1393 (SE = 0.1993)
tau (square root of estimated tau^2 value): 0.3732
I^2 (residual heterogeneity / unaccounted variability): 63.96%
H^2 (unaccounted variability / sampling variability): 2.77
R^2 (amount of heterogeneity accounted for): 67.96%

Test for Residual Heterogeneity:
QE(df = 4) = 11.0981, p-val = 0.0255

Test of Moderators (coefficients 2:5):
QM(df = 4) = 12.9783, p-val = 0.0114

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub	
intrcpt	0.2470	0.3001	0.8231	0.4104	-0.3411	0.8351	
severity Mild	1.7749	0.5124	3.4639	0.0005	0.7706	2.7792	***
severity Mild to moderate	0.0835	0.5333	0.1566	0.8756	-0.9618	1.1288	
severity Moderate	0.3037	0.6051	0.5018	0.6158	-0.8824	1.4897	
total dosage	0.0000	0.0001	0.8675	0.3857	-0.0001	0.0001	

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Mixed-Effects Model (k = 9; tau^2 estimator: DL)

tau^2 (estimated amount of residual heterogeneity): 0.0967 (SE = 0.1856)
tau (square root of estimated tau^2 value): 0.3109
I^2 (residual heterogeneity / unaccounted variability): 37.84%
H^2 (unaccounted variability / sampling variability): 1.61
R^2 (amount of heterogeneity accounted for): 77.77%

Test for Residual Heterogeneity:
QE(df = 4) = 6.4345, p-val = 0.1690

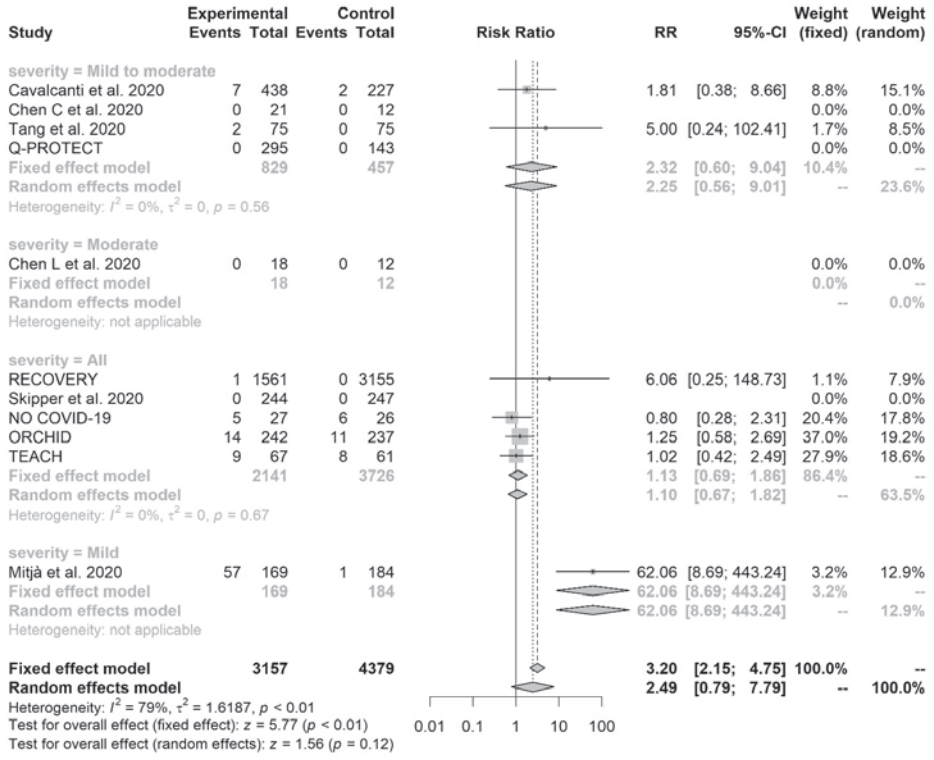
Test of Moderators (coefficients 2:5):
QM(df = 4) = 16.4805, p-val = 0.0024

Model Results:

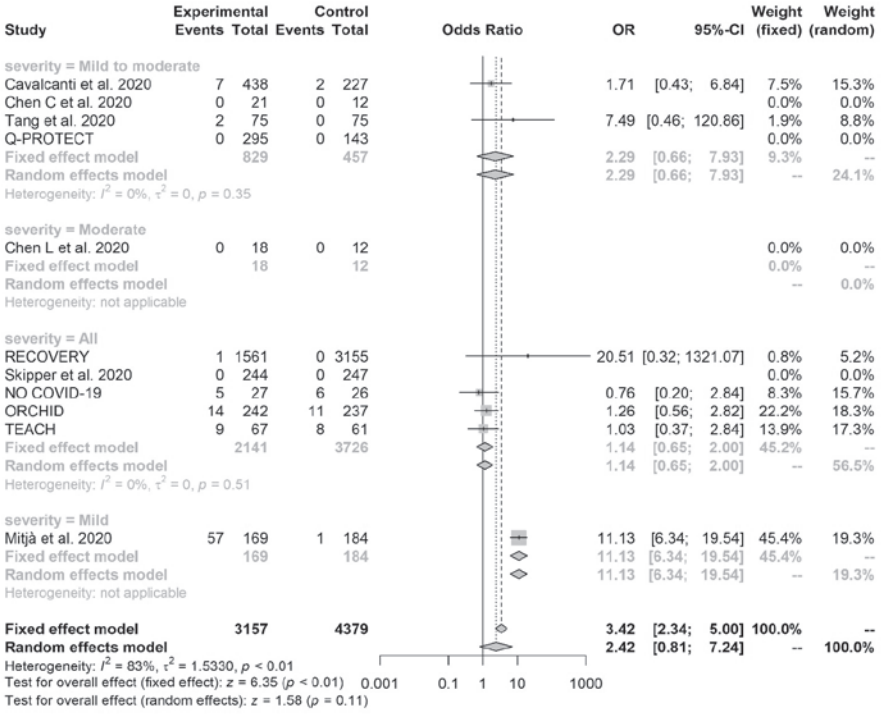
	estimate	se	zval	pval	ci.lb	ci.ub	
intrcpt	-0.3857	0.9795	-0.3938	0.6937	-2.3055	1.5340	
severity Mild	1.9235	0.4805	4.0028	<.0001	0.9817	2.8653	***
severity Mild to moderate	0.1159	0.6989	-0.1658	0.8683	-1.4858	1.2541	
severity Moderate	0.4418	0.5966	0.7404	0.4590	-0.7276	1.6112	
daily dosage	0.0016	0.0020	0.7968	0.4256	-0.0023	0.0054	

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Appendix N. Sensitivity analysis method to aggregate data: serious adverse events using the Mantel–Haenszel method



Appendix O. Sensitivity analysis method to aggregate data: serious adverse events using the Peto's method



Appendix P. Meta-regression for serious adverse event outcomes

Mixed-Effects Model (k = 7; tau^2 estimator: DL)

tau^2 (estimated amount of residual heterogeneity): 0 (SE = 0.6486)
tau (square root of estimated tau^2 value): 0
I^2 (residual heterogeneity / unaccounted variability): 0.00%
H^2 (unaccounted variability / sampling variability): 1.00
R^2 (amount of heterogeneity accounted for): 100.00%

Test for Residual Heterogeneity:
QE(df = 1) = 0.8720, p-val = 0.3504

Test of Moderators (coefficients 2:6):
QM(df = 5) = 16.5752, p-val = 0.0054

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub	
intrcpt	-0.3018	0.7029	-0.4294	0.6676	-1.6795	1.0758	
follow up 15 days	0.1768	2.8437	0.0622	0.9504	-5.3966	5.7503	
follow up 28 days	0.4409	0.5387	0.8185	0.4131	-0.6149	1.4967	
severity Mild	3.7955	1.0755	3.5290	0.0004	1.6875	5.9035	***
severity Mild to moderate	0.3818	2.9630	0.1289	0.8975	-5.4255	6.1892	
total dosage	0.0001	0.0002	0.3681	0.7128	-0.0003	0.0004	

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Mixed-Effects Model (k = 7; tau^2 estimator: DL)

tau^2 (estimated amount of residual heterogeneity): 0.0045 (SE = 1.1787)
tau (square root of estimated tau^2 value): 0.0672
I^2 (residual heterogeneity / unaccounted variability): 0.54%
H^2 (unaccounted variability / sampling variability): 1.01
R^2 (amount of heterogeneity accounted for): 99.46%

Test for Residual Heterogeneity:
QE(df = 1) = 1.0055, p-val = 0.3160

Test of Moderators (coefficients 2:6):
QM(df = 5) = 16.3419, p-val = 0.0059

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub	
intrcpt	-0.1232	0.9899	-0.1245	0.9009	-2.0634	1.8169	
follow up 15 days	-0.6162	1.8292	-0.3369	0.7362	-4.2013	2.9690	
follow up 28 days	0.3978	0.5720	0.6953	0.4868	-0.7234	1.5190	
severity Mild	3.8210	1.0778	3.5451	0.0004	1.7085	5.9335	***
severity Mild to moderate	1.2698	1.7057	0.7444	0.4566	-2.0734	4.6129	
daily dosage	0.0001	0.0016	0.0497	0.9603	-0.0031	0.0033	

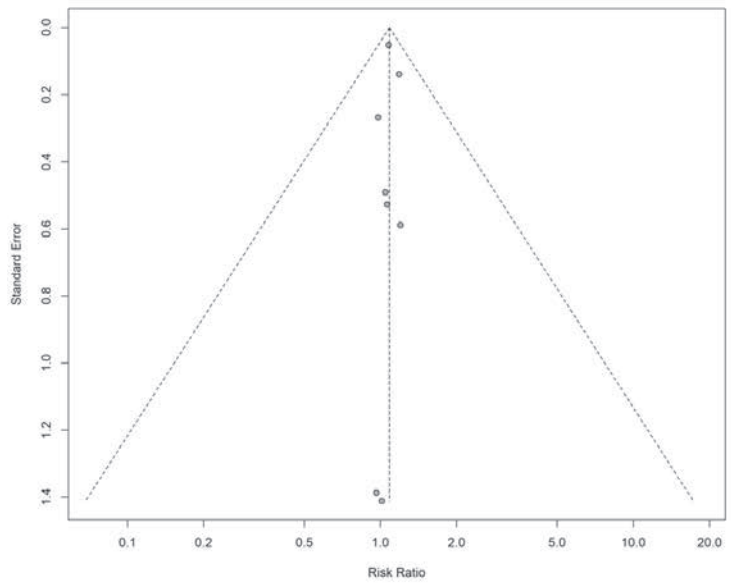
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Appendix Q. Risk of bias in the included studies

Study	Outcomes			
	Mortality	Cure	Adverse events	Serious adverse events
Abd-Elsalam *et al.* 2020	SC	SC	-	-
Cavalcanti *et al.* 2020	LRoB	-	SC	LRoB
Chen C *et al.* 2020	SC	SC	-	SC
Chen L *et al.* 2020	HRoB	HRoB	HRoB	HRoB
Chen J *et al.* 2020	HRoB	SC	HRoB	-
Chen Z *et al.* 2020	-	-	HRoB	-
RECOVERY	SC	-	-	SC
Kamran *et al.* 2020	-	HRoB	-	-
Mitjà *et al.* 2020	HRoB	-	HRoB	HRoB
Skipper *et al.* 2020	HRoB	-	HRoB	HRoB
Tang *et al.* 2020	HRoB	SC	HRoB	SC
NO COVID-19	HRoB	-	-	HRoB
Q-PROTECT	HRoB	HRoB	-	HRoB
ORCHID	LRoB	-	LRoB	LRoB
TEACH	SC	-	SC	SC
SOLIDARITY	SC	-	-	-

*HRoB=High Risk of Bias; SC=Some Concerns; LRoB=Low Risk of Bias.

Appendix R. Funnel plot and Egger's test of the mortality outcome at the most extended follow-up



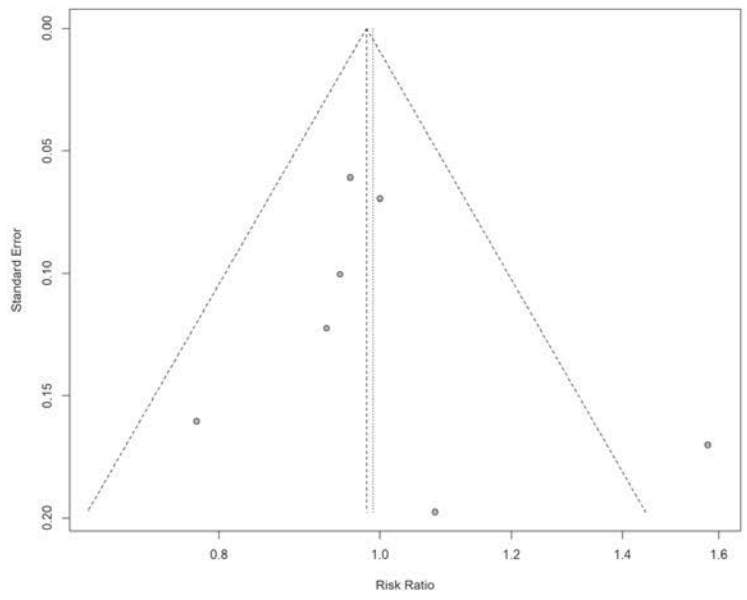
Linear regression test of funnel plot asymmetry

Test result: t = -0.00, df = 6, p-value = 0.9983

Sample estimates:

bias	se.bias	intercept	se.intercept
-0.0003	0.1439	0.0824	0.0192

Appendix S. Funnel plot and Egger's test of the cure outcome at the most extended follow-up



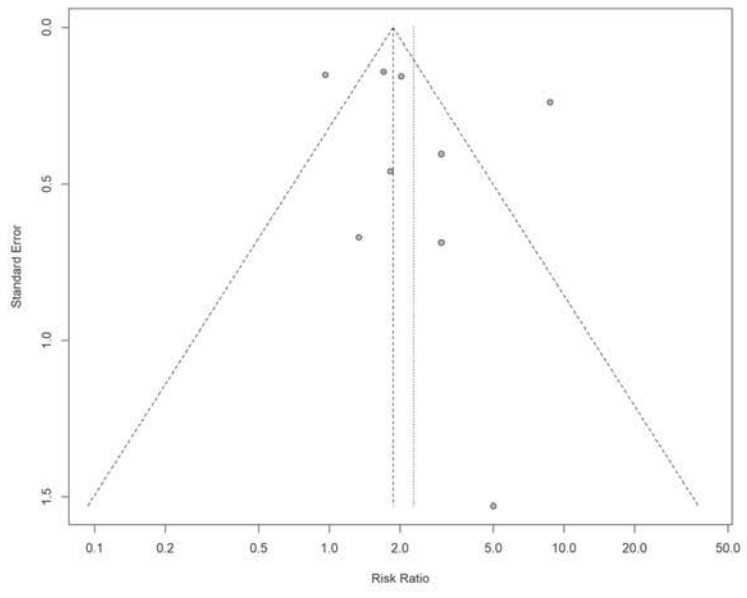
Linear regression test of funnel plot asymmetry

Test result: t = 0.58, df = 5, p-value = 0.5847

Sample estimates:

bias	se.bias	intercept	se.intercept
0.7845	1.3440	-0.0884	0.1305

Appendix T. Funnel plot and Egger's test of adverse event outcomes



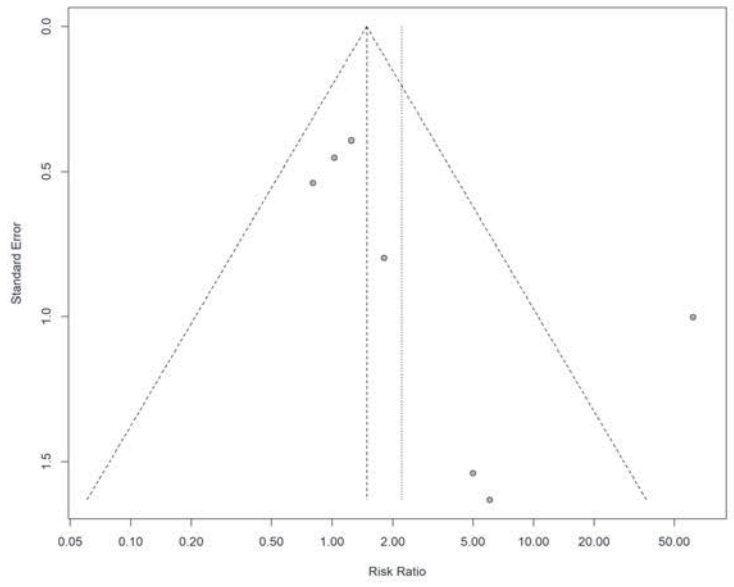
Linear regression test of funnel plot asymmetry

Test result: t = 0.81, df = 7, p-value = 0.4436

Sample estimates:

bias	se.bias	intercept	se.intercept
1.4308	1.7624	0.3476	0.4078

Appendix U. Funnel plot and Egger's test of serious adverse event outcomes



Linear regression test of funnel plot asymmetry

Test result: t = 1.96, df = 5, p-value = 0.1068

Sample estimates:

bias	se.bias	intercept	se.intercept
2.3625	1.2034	-0.9207	0.7468

Appendix V. GRADE assessment of outcomes

Outcome	# of participants	Methodological quality assessment					Risk of the event		RR	Quality of evidence
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Intervention	Control		
Mortality at the most extended follow-up	9392	0	0	0	0	0	577/4076	918/5316	1.09 (0.99-1.19)	High
Cure at the most extended follow-up	1375	-1	0	0	0	0	469/870	279/505	0.99 (0.89-1.10)	Moderate
Adverse events	2328	-1	0	0	-1	0	461/1266	166/1062	2.28 (1.36-3.83)	Low
Serious adverse events	7536	0	-1	0	-1	0	95/3157	28/4379	2.21 (0.89-5.47)	Low