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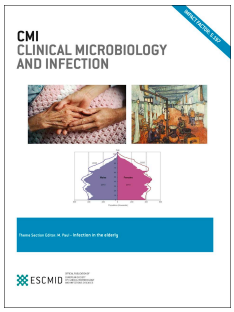

Effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients: a systematic review and meta-analysis

Thibault Fiolet, Anthony Guihur, Mathieu Rebeaud, Matthieu Mulot, Nathan Peiffer-Smadja, Yahya Mahamat-Saleh

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Title: Effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients: a systematic review and meta-analysis

Thibault Fiolet[1, 2*], Anthony Guihur[3], Mathieu Rebeaud[3], Matthieu Mulot[4], Nathan Peiffer-Smadja[5,6,7], Yahya Mahamat-Saleh[1, 2]

[1]CESP (Center for Research in Epidemiology and Population Health), Fac. de médecine - Univ. Paris-Sud, Fac. de médecine - UVSQ, INSERM, Université Paris Saclay, 94 805, Villejuif, France

[2]Gustave Roussy, F-94805, Villejuif, France

[3]Department of Plant Molecular Biology, Faculty of Biology and Medicine, University of Lausanne, Switzerland

[4] Laboratory of Soil Biodiversity, Faculty of Science, University of Neuchâtel, Switzerland.

[5]Université de Paris, IAME, INSERM, F-75018 Paris, France.

[6]National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, Imperial College London, London, UK.

[7]Infectious and Tropical Diseases Department, Bichat-Claude Bernard Hospital, AP-HP, Paris, 75018, France.

Corresponding author:

*Thibault Fiolet, MSc, PhD candidate in Epidemiology

Center for Research in Epidemiology and Population Health

Inserm U1018 “Health across Generations” Team and Paris-Sud 11 University/Paris-Saclay University

114 rue Edouard Vaillant

94805 Villejuif Cedex

Tel: (+33) 1-42-11-56-45 / Mobile: (+33) 6-79-50-91-19

E-mail: Thibault.fiolet@gustaveroussy.fr

Twitter: @T_Fiolet

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Abstract

Background

Hydroxychloroquine or chloroquine with or without azithromycin have been widely promoted to treat COVID-19 following early *in vitro* antiviral effects against SARS-CoV-2

Objective

The aim of this systematic review and meta-analysis was to assess whether chloroquine or hydroxychloroquine with or without azithromycin decreased COVID-19 mortality compared to the standard of care

Data sources

Pubmed, Web of Science, Embase Cochrane Library, Google Scholar and MedRxiv were searched until 25 July 2020

Study eligibility criteria

We included published and unpublished studies comparing the mortality rate between patients treated with chloroquine or hydroxychloroquine with or without azithromycin and patients managed with standard of care

Participants

Patients ≥18 years old with confirmed COVID-19

Interventions

Chloroquine or hydroxychloroquine with or without azithromycin

Methods

Effect sizes were pooled using a random-effects model. Multiple subgroup analyses were conducted to assess the drug safety

Results

The initial search yielded 839 articles, of which 29 articles met our inclusion criteria. All studies except one were conducted on hospitalized patients and evaluated the effects of hydroxychloroquine with or without azithromycin. Among the 29 articles, 3 were randomized controlled trials (RCT), one was a non-randomized trial and 25 were observational studies, including 10 with a critical risk of bias

and 15 with a serious or moderate risk of bias. After excluding studies with critical risk of bias, the meta-analysis included 11,932 participants for the hydroxychloroquine group, 8,081 for the hydroxychloroquine with azithromycin group and 12,930 for the control group. Hydroxychloroquine was not significantly associated with mortality: pooled Relative Risk RR=0.83 (95% CI: 0.65-1.06, n=17 studies) for all studies and RR=1.09 (95% CI: 0.97-1.24, n=3 studies) for RCTs. Hydroxychloroquine with azithromycin was associated with an increased mortality: RR=1.27 (95% CI: 1.04-1.54, n=7 studies). We found similar results with a Bayesian meta-analysis.

Conclusion

Hydroxychloroquine alone was not associated with reduced mortality in hospitalized COVID-19 patients but the combination of hydroxychloroquine and azithromycin significantly increased mortality.

Abbreviations: HCQ: Hydroxychloroquine; AZI: Azithromycin; CI: Confidence Interval; RR: Relative Risk; HR: Hazard Ratio, OR: Odds Ratio; RCT: Randomized Controlled Trial; US FDA: US Food and Drug Administration; EMA: European Medicine Agency

Introduction

On December 31, 2019, the World Health Organization (WHO) identified an unknown pneumonia caused by a new coronavirus, SARS-CoV-2, in Wuhan, China. By July 30, 2020, WHO confirmed more than 17 million cases and 667,935 deaths [1]. Chloroquine (CQ) and its derivative hydroxychloroquine (HCQ) were rapidly identified as potential drug candidates since CQ had an antiviral activity against Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) in vitro [2]. An *in vitro* antiviral activity of the aminoquinolines HCQ and CQ was confirmed against SARS-CoV-2 and a study reported a synergistic effect of the HCQ with azithromycin (AZI) against SARS-CoV-2 [3]. These drugs appeared as potential low-cost treatments for COVID-19 patients [4–7] and received wide and speculative coverage by the international press and the United States President [8].

Subsequently, HCQ and AZI were tested in a study where macaques were infected by SARS-CoV-2 and received either a high dose of HCQ (90 mg/kg on day 1 then 45 mg/kg) or a low HCQ dose (30 mg/kg on day 1 then 15 mg/kg) [9]. HCQ with or without AZI did not improve the time to viral clearance regardless of the stage of disease: prophylaxis, early treatment or late treatment.

Among the on-going trials, CQ or HCQ are among the most studied drugs [10,11]. Until today, most of the published studies on HCQ with a comparative group (standard care) were observational and non-randomized with inconsistent results [12–18]. Given the magnitude of the COVID-19 pandemic and the need for effective therapeutics, timely meta-analyses can play an important role in assessing the impacts of CQ and HCQ comparatively with standard of care on reliable clinical outcomes such as mortality. Previous meta-analyses on COVID-19 included a limited number of studies and used unadjusted risk ratios [19–21].

The aim of this systematic review and meta-analysis was to assess whether chloroquine or hydroxychloroquine with or without azithromycin decreased the mortality of COVID-19 compared to standard of care.

Methods

The research question was: in patients with confirmed COVID-19, is the addition of hydroxychloroquine or chloroquine with or without azithromycin to the standard of care, effective in improving survival?

PICO question:

Population: patients with confirmed COVID-19

Intervention: HCQ or CQ, with or without AZI

Comparison: a standard of care

Outcomes: the survival rate of COVID-19 patients

Data sources, search strategy

A search was performed using PubMed, Web of Science, Embase and Cochrane Review up to July 25, 2020 with the following string search: (COVID-19 OR SARS-CoV-2) AND (MORTALITY OR DEATH) AND (HYDROXYCHLOROQUINE OR HCQ) (Supplementary text S1). Given that the number of articles about HCQ and COVID-19 is rapidly growing, we also manually searched for additional references on the MedRxiv preprint server and on Google Scholar with the same terms. An additional search on PubMed, Web of Science and Cochrane Review was conducted for chloroquine with the search terms described in Supplementary materials S1: (COVID-19 OR SARS-CoV-2) AND (MORTALITY OR DEATH) AND (CHLOROQUINE OR CQ). This meta-analysis was conducted following PRISMA statements in Supplementary text S2. This study has been recorded on the international database of prospectively registered systematic reviews, PROSPERO (Registration number: CRD42020190801).

Study selection:

Study selection was conducted by two investigators (TF and YM) who screened the titles and the abstracts. Discrepancies were resolved by a third investigator (AG). Inclusion criteria were 1) reports containing original data with available risk estimates (Hazard Ratios, Odds Ratios, Relative Risk and/or with data on the number of deaths in HCQ/CQ and control groups; 2) any publication dates; 3) comparative studies with a control group without HCQ nor CQ; and 4) COVID-19 confirmed cases by

RT-PCR. Studies reporting no deaths, reviews and meta-analyses, commentaries, editorials and *in vitro* and *in vivo* animal studies were excluded.

Data extraction

Two investigators (TF and YM) extracted the following data for each study: study design, publication date, journal, location, number of participants and deaths (in treatment and control groups), HCQ or CQ doses when available, effect size (Hazard Ratio, Odds Ratio or Relative Risk) and 95% confidence intervals for reported risk estimates. The estimates from the model, adjusted for the maximum number of covariates were used to control potential confounders, according to Cochrane Methodology [22]. For each study, risk factors associated with higher mortality were taken into account through the reported adjusted effect sizes.

When studies did not report an effect size for mortality risk [17,23,24],we used the number of deaths per group to calculate an unadjusted relative risk using *metabin* function in *meta* package in R Software [25].

For all the other studies, reported adjusted OR, RR or HR were used.

Individual risk of bias

The quality of each study was assessed with ROBIN-I tool following Cochrane guidelines for non-randomized studies and with Rob2 for randomized studies [26,27].

Outcome

The outcome was the mortality of COVID-19 patients.

Statistical analysis

Effect of CQ/HCQ alone and HCQ + AZI

A primary meta-analysis was performed to compare the survival rate (or mortality) between patients treated with CQ or HCQ and standard of care. Then, the relationship between HCQ associated with

AZI and mortality was assessed. HRs, ORs and RRs were treated as equivalent measures of mortality risk. Pooled RRs were determined by using a random effect model with inverse variance weighting (DerSimonian-Laird method) [28]. Significance was checked using a Z-test, where $p<0.05$ is considered as significant. The absolute risk difference was calculated from the UK baseline hospital mortality risk of 26% (according to ISARIC WHO CCP-UK cohort based on 20,133 patients) using the formula $RD = BR \times (RR-1)$ [29].

Heterogeneity was assessed by the Cochrane Q test and I^2 test [30]. $30\%<I^2<60\%$ was interpreted as moderate heterogeneity and $I^2>60$ as substantial heterogeneity. A funnel plot was constructed to assess the publication bias. Begg's and Egger's tests were conducted to assess the publication bias [31,32]. RR or HR were used to assessed mortality risk within a 95% confidence interval. In the main analysis, studies with critical bias were excluded. A sensitivity analysis including these studies, was conducted. A Bayesian meta-analysis was performed to test the robustness of our results, allowing incorporation of full uncertainty in all parameters [33]. The traditional random-effect model has fixed parameters for the distribution of the true treatment effect RR with an unknown mean θ, within-study variance σ^2 and between study variance τ^2. The Bayesian random-effect model assumes these parameters are random with a probability distribution. Two prior distributions were tested $\mu \sim$ Normal (1,100) with a large variance and $\tau \sim$ Half-Cauchy (0,0.5) and a second scenario with $\mu \sim$ Normal (1,1) and $\tau \sim$ Half-Cauchy (0,0.5). The Bayesian analysis was conducted with the R package "brms" [34].

Subgroup analysis

Subgroup analyses were further conducted according to the quality assessment to explore the source of heterogeneity among observational studies. We performed stratified analyses by type of article (peer-reviewed vs unpublished), use of an adjustment on confounding factors (studies with $RR_{unadjusted}$ vs $RR_{adjusted}$), mean daily dose of HCQ or CQ (continuous), median population age across the studies, level of bias risk identified with ROBIN-I (moderate/serious/critical) [26] and when we excluded studies with cancer and dialysis patients. Mean daily dose of HCQ or CQ was the daily average

between the loading dose and the maintenance doses. Additionally, influence analysis was conducted by omitting each study to find potential outliers [34]. Influence analysis is used to detect studies which influence the overall estimate of a meta-analysis the most, omitting one study at a time (leave-one-out method).

A two-sided p-value <0.05 was considered statistically significant. All analysis were conducted using R version 3.6.1 with *meta* package and *robvis* package [35].

Results

Literature Search

A flow chart is presented in Figure 1. After searching Pubmed, Cochrane Review and Web of Science, 839 articles were identified. After screening the title and the abstract, only 21 articles about hydroxychloroquine and COVID-19 were included for further consideration. We excluded 564 articles that did not meet the inclusion criteria. We did not find any non-English articles meeting our inclusion criteria. Two duplicate studies on the same cohort were excluded [12,36]. Two Chinese randomised controlled trials on hydroxychloroquine reported zero deaths in both treatment and control groups [37,38] and thus their results were not included in our meta-analysis. Ten articles from Medrxiv/Google Scholar were added. Thus, 29 articles were included, of which 25 were observational studies, one was an interventional non-randomized study and three were randomized controlled trials (RCT). These studies included27 articles for HCQ [14–19,23,24,36,39–56] and 12 articles for HCQ+AZI [18,36,41,42,47,48,50,51,57–60]. For CQ, after searching Pubmed, Cochrane Review, Embase and Web of Science, 449 articles were identified. After screening the title and the abstract, only 1 Brazilian RCT and 3 observational studies studied chloroquine and COVID-19. However, among these studies, Gabriela Silva Borba et al. and Saleh et al. studies did not have a standard of care comparative group [61,62]. Khamis et al. did not report death data related to chloroquine and Huang et al. did not report any death [63,64]. Consequently, no study on chloroquine met our inclusion criteria.

Study characteristics

This meta-analysis included 15,190 patients in the HCQ group, 8081 patients in the HCQ with AZI and 14,060 patients in the standard of care group with 3,152 deaths, 1,063 deaths and 2,857 deaths, respectively. Individual studies are described in Tables S1 and S2. All included studies except one (Skipper et al.) were carried out on hospitalized patients [39]. Mean (± SD) age of participants was 62.1 ± 8.5 years. Ten studies were conducted in the USA [15,18,23,41,42,49,50,53,56,58], 4 in Spain [16,17,44,57], 7 in France [13,24,46,48,54,59,60], one in the UK [40], two in Italy [43,65], one in China [14], one in Brazil [51] and three in several other countries (USA, Canada, Italy and Spain)[39,47,52]. Twenty-two articles were published [13–15,17,18,24,39,41,43,44,46,49–54,56,57,59,60,65], and 6 articles were preprints [16,23,40,42,48,58]. Mean daily dose of HCQ ranged from 333 mg/j to 945 mg/j. Few studies precisely described concomitant use of corticosteroids (Table S3) [15–17,44,48,50–52,65]. Only the RECOVERY trial precisely reported the use of dexamethasone (8% vs 9% in both arms) [40].

Study quality

Risk of bias was assessed with ROBIN-I for non-randomised studies (n=26) and Rob2 for RCT (n=3) (Figures S1-S2). Three RCT had some concerns [39,40,51] and one interventional non-randomized study had critical risk of bias [24]. Among the observational studies, fifteen articles had a moderate or serious risk of bias [13–18,41,42,44,46–48,56,58] and ten studies had a critical risk of bias [23,43,49,50,52–54,59,60,65]. Eleven observational studies did not report adjusted effect sizes to control confusion and selection bias [23,24,43,44,49,53,54,57,59,60,65]. Quality of studies was lowered by the lack of information about the assignment of treatment, the time between start of follow-up and start of intervention), some unbalanced co-intervention with other antiviral and antibiotic drugs and imbalance between groups for confounders such as comorbidities and age.

Hydroxychloroquine and mortality

After excluding studies with critical bias, the pooled RR for COVID-19 mortality was 0.83 (95%CI: 0.65-1.06, n=17 studies) indicating no significant association between HCQ and COVID-19 mortality (Figure 2). Under the hypothesis of having a baseline mortality risk of 26% (based on ISARIC WHO

CCP-UK cohort [29]), these pooled relative risk values would correspond to a non-significant risk difference of -4.4% [29] (Table 1). There was a significant subgroup difference between RCT and non-randomized studies ($P_{heterogeneity\ between}$ = 0.03) with respectively RR_{RCT}=1.09 (95%CI: 0.97-1.24) and $RR_{non\text{-}randomized}$= 0.79 (95%CI: 0.60-1.04) (Figure 2). Among observational studies with a moderate risk of bias, we found no association between HCQ and mortality $RR_{moderate\ bias}$=1.03 (95%CI: 0.91-1.17, I^2=0%, n=7 studies) with no subgroup heterogeneity (Table S4, Figure S3). Results remained nonsignificant with influence analysis (Figure S4). The Bayesian meta-analysis led to similar results with a pooled RR for mortality of 0.93 (95%CI: 0.72-1.14, n=17 studies) (Table S5, Figure S5). In sensitivity analysis, after inclusion of studies with critical risk of bias, the global RR was marginally not significant 0.80 (95%CI: 0.65-1.00) (Table S6).

Outcome: all-cause mortality	Number of studies	Pooled Relative Risk	Risk difference
Hydroxychloroquine alone			
All studies	17	0.83 [0.65-1.06]	-4.4% [-9% ; +1.5%]
Non-randomized studies	14	0.79 [0.60-1.04]	-5.5% [-10% ; +1%]
Randomized studies	3	1.09 [0.97-1.24]	+2.3% [-0.8% ; +6.2%]
Hydroxychloroquine with azithromycin			
All studies	7	1.27 [1.04-1.54]	+7% [+1% ; +14%]
Non-randomized studies	6	1.29 [1.06-1.58]	+7.5% [+1.6% ; +15%]
Randomized studies	1	0.64 [0.18-2.24]	-9% [-21% ; +32%]

Table 1: Relative risk and risk difference for mortality associated with hydroxychloroquine with or without azithromycin, assuming a UK mortality rate in hospital of 26% according to ISARIC WHO CCP-UK cohort.

There was a significant higher heterogeneity among non-randomised studies as compared to RCT (I^2 =84%, $P_{heterogeneity\ within}$<0.01). In fact, heterogeneity was null for RCT. Egger's test (p= 0.68) and Begg's test (P=0.13) were not significant for asymmetry of the funnel plot indicating that there was no major publication bias for non-randomized studies (Figure S6).

Hydroxychloroquine with azithromycin and mortality

After exclusion of studies with critical bias, the pooled RR for COVID-19 mortality was 1.27 (95%CI: 1.04-1.54, n=7) indicating an increased mortality linked to the use of hydroxychloroquine with azithromycin. With a baseline hospital mortality of 26%, we identified a significant absolute risk difference of +7%. We found an increased risk of mortality in patients treated with hydroxychloroquine and azithromycin compared to standard of care (RR: 1.29 (95%CI: 1.06-1.58, n=6)) among non-randomized studies but this relationship was not found in the single Brazilian RCT, with no heterogeneity observed across the study design ($P_{\text{heterogeneity between}} = 0.28$) (Figure 3). There was a low heterogeneity across the included studies ($I^2 = 38\%$, p=0.14). Egger's test (p= 0.70) and Begg's test (p=0.65) were not significant but the asymmetry in the funnel plot indicates that a publication bias could be present (Figure S7). However, the number of included studies was small. Subgroup analyses are described in supplementary material (Table S4, Figure S8). The Bayesian meta-analysis led to similar results with a pooled RR for mortality of 1.32 (95%CI: 0.97-1.68, n=7 studies) (Table S5, Figure S9). The increase in mortality was also significant with influence analysis (Figure S10).

Discussion

This meta-analysis summarized the results of 25 observational studies, three randomised controlled trials and one interventional non-randomised study on the effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients (Table 1). Despite our inclusion criteria that did not specify the stage of the disease, all the studies were conducted with hospitalized patients except the RCT by Skipper et al. RCT [39]. Our results show that while hydroxychloroquine alone was not associated with reduced mortality in COVID-19 patients, the combination of hydroxychloroquine and azithromycin significantly increased mortality. We found similar results with a Bayesian analysis.

Our meta-analysis reported a high heterogeneity for hydroxychloroquine alone, but this heterogeneity was lowered among RCT, studies with moderate risk of bias and for the association of HCQ+AZI. The various quality of studies (not reporting HCQ dose, the lack of adjustment in reported estimates) may explain one part of the heterogeneity observed according to our subgroup analysis (Table S4).

A previous systematic review only included 8 studies on all-cause mortality in COVID-19 patients [13–16,23,38,41,66] and concluded that the level of evidence for hydroxychloroquine effect was very weak[67]. A preprint meta-analysis, using routinely collected records from clinical practice in Germany, Spain, the UK, Japan, and the USA, compared the use of HCQ with sulfasalazine [68]. This study observed an increased risk of 30-day cardiovascular mortality (HR=2.19 [1.22-3.94]), although the study lacked a standard of care comparative group. Some previous meta-analyses were also conducted on hydroxychloroquine and various health endpoints including mortality. However these studies did not report all the published and unpublished literature, including a very limited number of studies: from 3 articles[19,20] to 6 articles[21]. These previous meta-analyses did not perform subgroup and sensitivity analysis to test the effect of pooling RCT and observational study, nor did they study the source of heterogeneity. They used unadjusted risk ratio (calculated with the number of events in each group) whereas in our meta-analysis, we used adjusted relative risk [69] and we ran sensitivity analysis on the adjustment of effect size. Statistical adjustments for key prognostic variables limit confusion bias, especially in observational studies which are not randomised. This meta-analysis confirmed the partial preliminary results of these other meta-analyses about the absence of effect for HCQ on survival and found an increased mortality with the use of the combination of HCQ with AZI in COVID-19 patients. These results confirm the preliminary findings of several observational studies which have shown that the combination of hydroxychloroquine and azithromycin might increase the risk of acute, life-threatening cardiovascular events [70]. A first study found that, among patients treated with this combination, 6 out of 18 (33%) developed a significant increase in the QTc interval.[71] Another work found that in 84 patients treated with HCQ + AZI, 9 had a severe prolongation of QTc [72]. The combination of HCQ + AZI was associated with a greater variation in the QTc interval compared to hydroxychloroquine alone in a study with 90 patients [73]. In a study conducted in New York on 1438 patients cardiac arrest was significantly more likely in patients receiving hydroxychloroquine with azithromycin compared to patients receiving neither of the two drugs (adjusted OR, 2.13 [95% CI, 1.12-4.05]) [18]. Finally, a study conducted on the WHO

database bringing together more than 167,000 patients found an increased risk of potentially fatal acute cardiac events in patients treated with azithromycin alone or with hydroxychloroquine alone [74]. The combination of the two drugs posed an even greater risk of life-threatening acute cardiac effects [18,73,74].

Several national health organisations (US FDA Food and Drug Administration[75], French Agency for the Safety of Health Products ANSM [76], European Medicine Agency EMA [77]) raised concerns about using unapproved drugs for COVID-19. ANSM and US FDA removed the authorization for the use of HCQ outside of clinical trials. The Indian Council of Medical Research took the opposite position and recommended chemoprophylaxis with hydroxychloroquine for asymptomatic cases [78]. Finally, in the comparative peer-reviewed studies, a clear conclusion on hydroxychloroquine is not possible due to the small sample size, the lack of well-performed randomised controlled trials (mainly non-randomised and retrospective studies) and inconsistent results. Many preprints without a comparative group and without randomization added to confusion surrounding this highly politicised topic[79]. There is a gap between the speed of clinical research and the expectation of a clear solution to treat COVID-19 patients. Indeed, producing robust clinical trials is necessarily time-consuming. In a press communication, on 20 June 2020, US National Institutes of Health (NIH) stopped the clinical trial of hydroxychloroquine since this drug was very unlikely to be efficient to treat COVID-19 patients [80]. Based on SOLIDARITY trial results, WHO previously undertook the same decision [81].

A Bayesian meta-analysis confirmed our findings from classical random-effect meta-analysis. We included several unpublished papers to minimize the publication bias. Our subgroup analysis by published studies (vs unpublished studies) found that the inclusion of preprints did not change the results. Exclusion of grey literature (unpublished studies, with limited distribution) could lead to an exaggeration of the intervention effect by 15% [82]. There is limited evidence to identify whether grey studies have a poorer methodological quality than published studies[83].

A major limitation is the inclusion of patients at different levels of COVID-19 severity. However, we could not conduct subgroup analysis for severity since most of studies reports do not use the same definition of severity and do not report the same biological and clinical outcomes. We also noted a high level of heterogeneity in the administration of HCQ (dosing, timing between hospital administration and intervention, duration…). In some studies, these data were not reported at all. Another limitation comes from the studies which did not report adjusted effect size when mortality was not the primary endpoint, leading to a high risk of confounding bias. As is usually done, this meta-analysis was based on aggregated data, without access to original patient data. Most of the included studies were observational which are not adapted to identify a causal association. Indeed, some of the included studies had very low quality of evidence (missing data, small sample size, confusion bias, bias in classification of intervention and selection bias), although our supplementary analyses and the exclusion of these articles did not change the results. Finally, this meta-analysis did not include results from the European DisCoVeRy trial and the WHO Solidarity trial that are not yet published or communicated [81].

In conclusion, this meta-analysis clearly shows that hydroxychloroquine alone is not effective for the treatment of COVID-19 patients and that the combination of hydroxychloroquine and azithromycin increases the risk of mortality. These data support current clinical recommendations such as those of the NIH [84] which do not recommend the use of HCQ alone or in combination with azithromycin for COVID-19 patients. There is already a great number of studies that have evaluated HCQ alone or in combination [10] and it seems unlikely at this stage that any efficacy will ever emerge. Our results suggest that there is no need for further studies evaluating these molecules, and the European DisCoveRy clinical trial or the WHO international Solidarity clinical trial have already discontinued treatment arms using hydroxychloroquine [81,85].

Conflict of interests: All authors declare: no support from any organisation for the submitted work other than that described above; no financial relationships with any organisations that might have an

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Contribution: TF designed the research. TF, MR, AG, MM, NPS and YMS conducted the research. TF did the statistical analysis. TF wrote the first draft of the paper. MR, AG, MM, NPS and YMS contributed to the writing of the paper. All authors contributed to the data interpretation, revised each draft for important intellectual content, and read and approved the final manuscript.

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List of figures

Figure 1: Flow diagram of study selection process

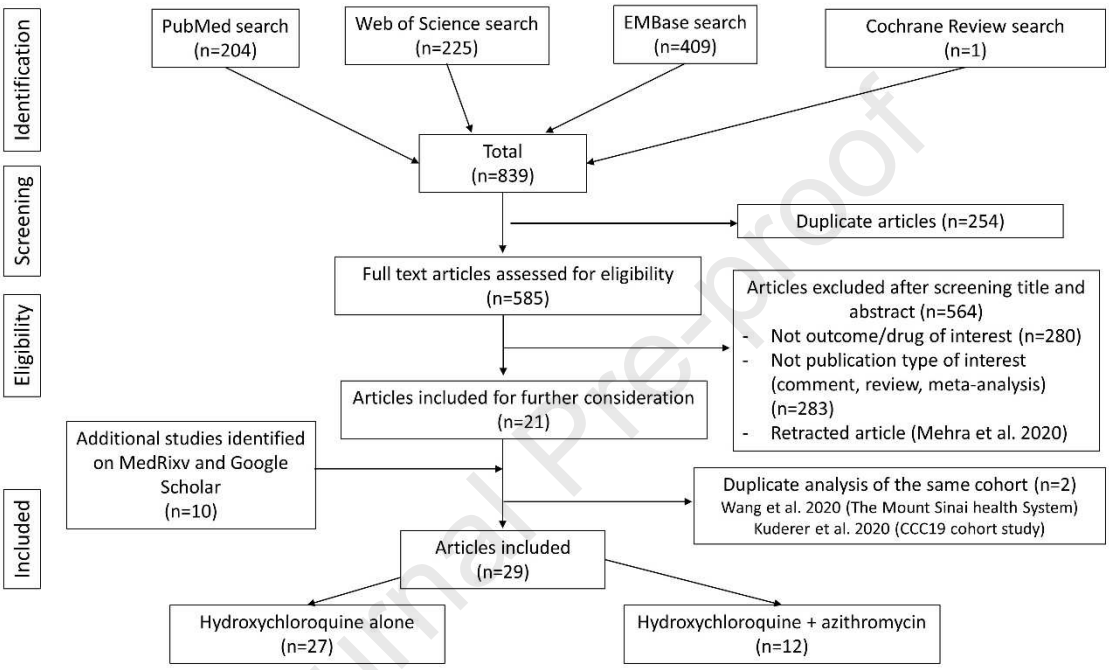

Figure 2: Forest plot of the association between hydroxychloroquine alone and COVID-19 mortality*

*Excluding studies with critical risk of bias
RR=Risk Ratio 95%-CI= 95% Confidence Interval

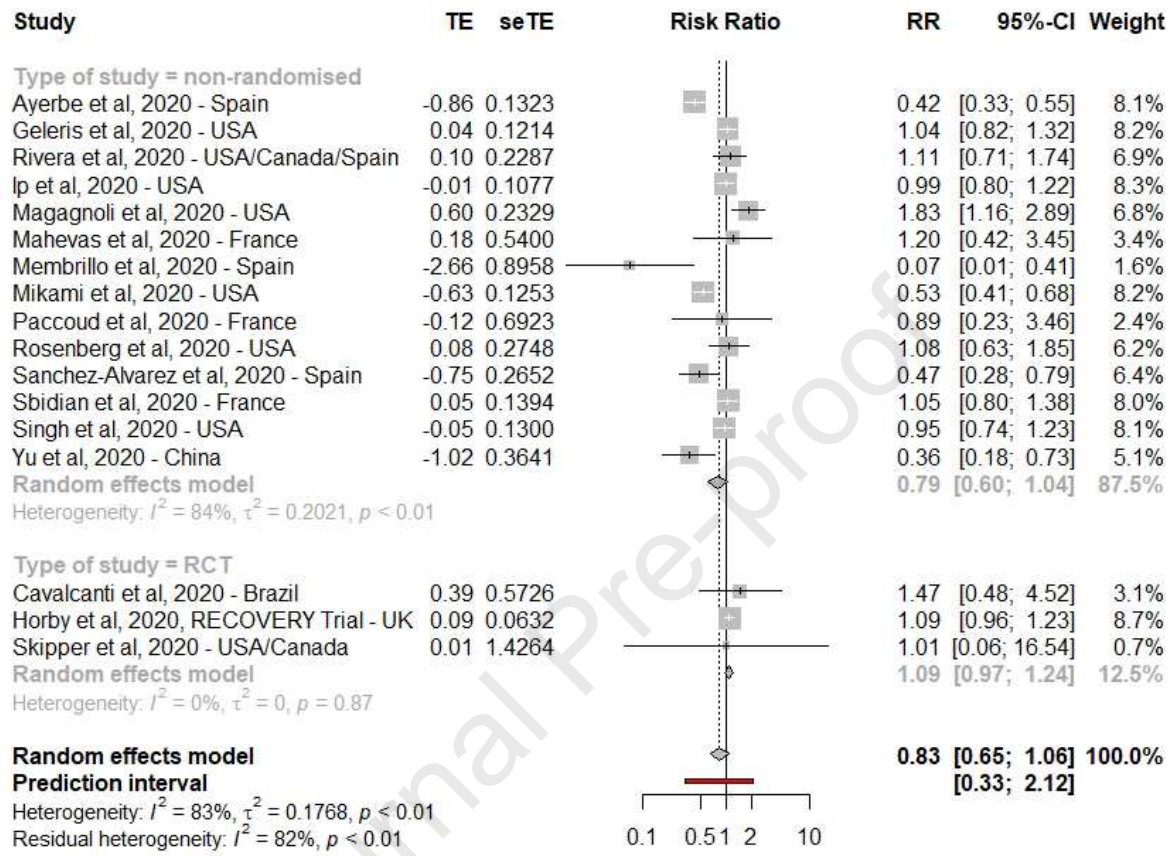

Figure 3: Forest plot of the association between hydroxychloroquine with azithromycin and COVID-19 mortality*

*Excluding studies with critical risk of bias
RR=Risk Ratio 95%-CI= 95% Confidence Interval