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Systematic review

Effect of hydroxychloroquine with or without azithromycin on the mortality of coronavirus disease 2019 (COVID-19) patients: a systematic review and meta-analysis

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ABSTRACT

Background: Hydroxychloroquine or chloroquine with or without azithromycin have been widely promoted to treat coronavirus disease 2019 (COVID-19) following early *in vitro* antiviral effects against severe acute respiratory syndrome coronavirus 2 (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 with the standard of care.
Data sources: PubMed, Web of Science, Embase Cochrane Library, Google Scholar and MedRxiv were searched up to 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Study eligibility criteria: We included published and unpublished studies comparing the mortality rate between patients treated with chloroquine or hydroxychloroquine with or without azithromycin and patients managed with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 drug safety.
Results: The initial search yielded 839 articles, of which 29 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, three were randomized controlled trials, one was a non-randomized trial and 25 were observational studies, including 11 with a critical risk of bias and 14 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, 8081 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 randomized controlled trials. 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.

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Conclusion: Hydroxychloroquine alone was not associated with reduced mortality in hospitalized COVID-19 patients but the combination of hydroxychloroquine and azithromycin significantly increased mortality. **Thibault Fiolet, Clin Microbiol Infect 2020;▪:1**

Introduction

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

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

Among the ongoing trials, chloroquine or hydroxychloroquine are among the most studied drugs [10,11]. Until today, most of the published studies on hydroxychloroquine 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 chloroquine and hydroxychloroquine compared 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 with standard of care.

Methods

The research question was: in individuals 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 hydroxychloroquine or chloroquine, with or without azithromycin.

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 25 July 2020 with the following string search: (COVID-19 OR SARS-CoV-2) AND (MORTALITY OR DEATH) AND (HYDROXYCHLOROQUINE OR hydroxychloroquine) (see Supplementary material, Text S1). Given that the number of articles about hydroxychloroquine 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 CQ with the search terms described in the Supplementary materials (Text S1): (COVID-19 OR SARS-CoV-2) AND (MORTALITY OR DEATH) AND (CHLOROQUINE OR chloroquine). This meta-analysis was conducted following the PRISMA statements in the Supplementary material (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 (a) reports containing original data with available risk estimates (hazard ratios (HR), odds ratios (OR), relative risk (RR) and/or with data on the number of deaths in hydroxychloroquine/chloroquine and control groups; (b) any publication dates; (c) comparative studies with a control group with no hydroxychloroquine nor chloroquine; and (d) PCR-confirmed cases of COVID-19. 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), hydroxychloroquine or chloroquine doses when available, effect size (HR, OR or RR) and 95% CI 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.

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Individual risk of bias

The quality of each study was assessed with the 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 chloroquine/hydroxychloroquine alone and hydroxychloroquine + azithromycin

A primary meta-analysis was performed to compare the survival rate (or mortality) between patients treated with chloroquine or hydroxychloroquine and standard of care. Then, the relationship between hydroxychloroquine associated with azithromycin and mortality was assessed. HR, OR and RR were treated as equivalent measures of mortality risk. Pooled RR 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 (RD) was calculated from the UK baseline hospital mortality risk (BR) 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 assess mortality risk within a 95% CI. 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 that these parameters are random with a probability distribution. Two prior distributions were tested μ~Normal (1,100) with a large variance and τ~Half-Cauchy (0,0.5) and a second scenario with μ~Normal (1,1) and τ~Half-Cauchy (0,0.5). The Bayesian analysis was conducted with the R package *brms* [34].

Subgroup analysis

Subgroup analyses were 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 versus unpublished), use of an adjustment on confounding factors (studies with $RR_{unadjusted}$ versus $RR_{adjusted}$), mean daily dose of hydroxychloroquine or chloroquine (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 hydroxychloroquine or chloroquine 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 that 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 analyses were conducted using R version 3.6.1 with *meta* package and *robvis* package [35].

Results

Literature search

A flow chart is presented in Fig. 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 randomized controlled trials (RCT) on hydroxychloroquine reported zero deaths in both treatment and control groups [37,38] and so their results were not included in our meta-analysis. Ten articles from Medrxiv/Google Scholar were added, so 29 articles were included, of which 25 were observational studies, one was an interventional non-randomized study and three were RCT. These studies included 27 articles for hydroxychloroquine [14–19,23,24,36,39–56] and 12 articles for hydroxychloroquine + azithromycin [18,36,41,42,47,48,50,51,57–60]. For chloroquine, after searching PubMed, Cochrane Review, Embase and Web of Science, 449 articles were identified. After screening the title and the abstract, only one Brazilian RCT and three observational studies described chloroquine and COVID-19. However, among these studies, those by Borba et al. and Saleh et al. did not have a standard of care comparative group [61,62]. Khamis et al. did not report death data related to CQ 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 hydroxychloroquine group, 8081 patients in the hydroxychloroquine with azithromycin group and 14 060 patients in the standard of care group with 3152 deaths, 1063 deaths and 2857 deaths, respectively. Individual studies are described in the Supplementary material (Tables S1 and S2). All included studies were carried out on hospitalized patients except for one [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], four in Spain [16,17,44,57], seven 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 [13–15,17,18,24,39,41,43,44,46,47,49–54,56,57,59,60,65] and six articles were preprints [16,23,40,42,48,58]. Mean daily dose of hydroxychloroquine ranged from 333 mg/day to 945 mg/day. Few studies precisely described concomitant use of corticosteroids (see Supplementary material, Table S3) [15–17,44,48,50–52,65]. Only the RECOVERY trial precisely reported the use of dexamethasone (8% versus 9% in both arms) [40].

Study quality

Risk of bias was assessed with ROBIN-I for non-randomized studies ($n = 26$) and Rob2 for RCT ($n = 3$) (see Supplementary material, Figs S1 and 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, fourteen articles had a moderate or serious risk of bias [13–18,41,42,44,46–48,56,58] and eleven studies had a critical risk of bias

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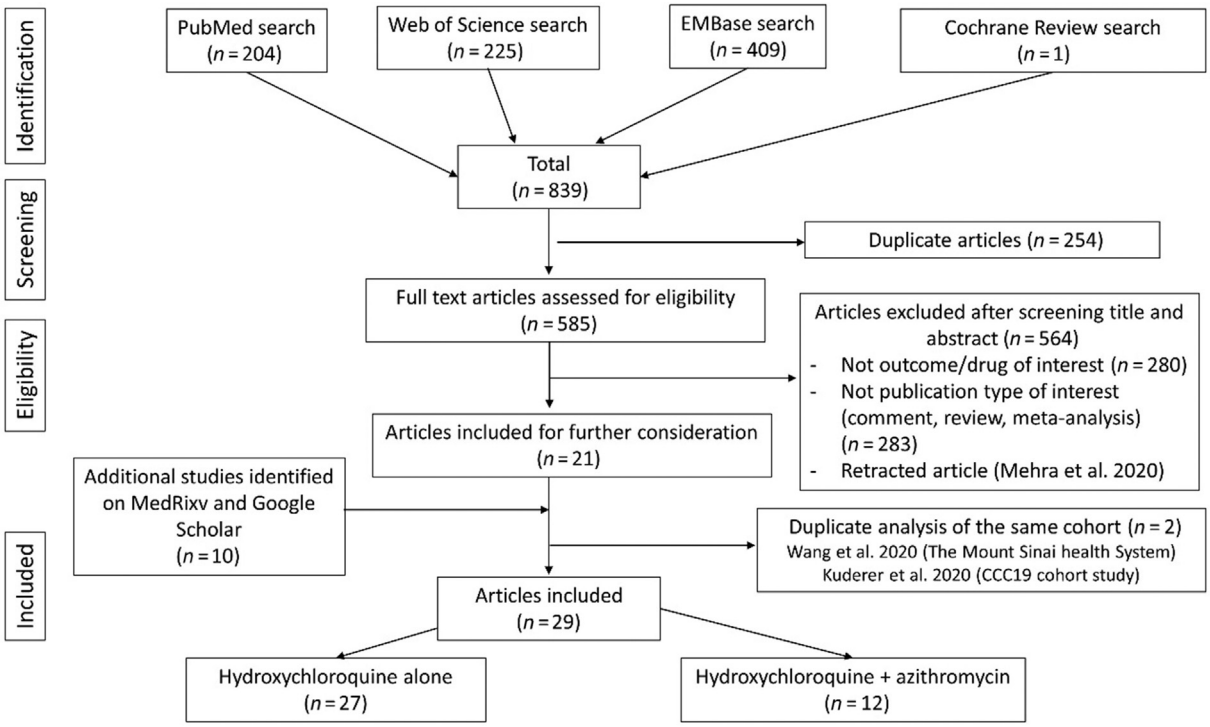

Fig. 1. Flow diagram of study selection process.

[23,43,49,50,52–54,57,59,60,65]. 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 co-morbidities 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 hydroxychloroquine and COVID-19 mortality (Fig. 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 ($P_{\text{heterogeneity between}} = 0.03$) with respectively $RR_{RCT} = 1.09$ (95% CI 0.97–1.24) and $RR_{\text{non-randomized}} = 0.79$ (95% CI 0.60–1.04) (Fig. 2). Among observational studies with a moderate risk of bias, we found no association between hydroxychloroquine and mortality $RR_{\text{moderate bias}} = 1.03$ (95% CI 0.91–1.17, $I^2 = 0\%$, $n = 7$ studies) with no subgroup heterogeneity (see Supplementary material, Table S4, Fig. S3). Results remained non-significant with influence analysis (see Supplementary material, Fig. 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) (see Supplementary material, Table S5, Fig. 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) (see Supplementary material, Table S6).

There was a significant higher heterogeneity among non-randomized studies compared with RCT ($I^2 = 84\%$, $P_{\text{heterogeneity within}} < 0.01$). 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 (see Supplementary material, Fig. 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 with 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 ($P_{\text{heterogeneity between}} = 0.28$) (Fig. 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 (see Supplementary material, Fig. S7). However, the number of included studies was small. Subgroup analyses are described in the Supplementary material (Table S4, Fig. 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) (see Supplementary material, Table S5, Fig. S9). The increase in mortality was also significant with influence analysis (see Supplementary material, Fig. S10).

Discussion

This meta-analysis summarized the results of 25 observational studies, three RCT and one interventional non-randomized study on the effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients (Table 1). Despite our

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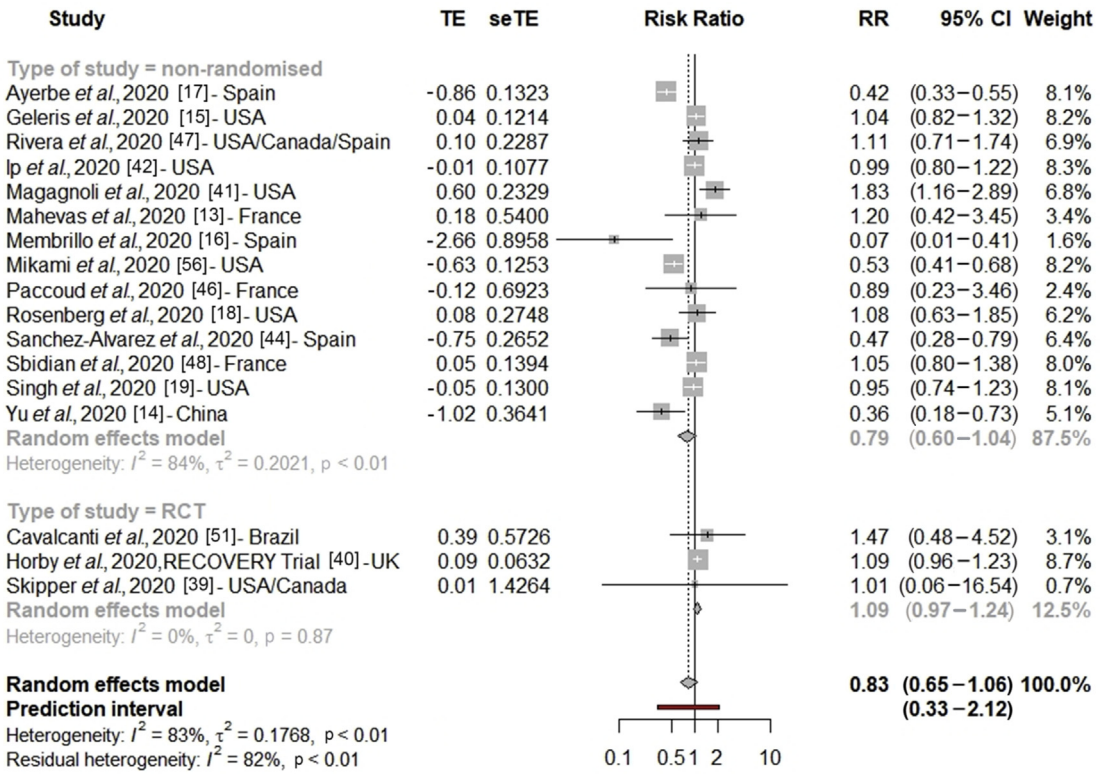

Fig. 2. Forest plot of the association between hydroxychloroquine alone and COVID-19 mortality (excluding studies with critical risk of bias). RR, risk ratio.

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. [39]. Our results show that hydroxychloroquine alone was not associated with reduced mortality in COVID-19 patients, but 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 hydroxychloroquine + azithromycin. The variable quality of the studies (not reporting hydroxychloroquine dose, the lack of adjustment in reported estimates) may explain one part of the heterogeneity observed according to our subgroup analysis (see Supplementary material, Table S4).

A previous systematic review only included eight studies on all-cause mortality in COVID-19 patients [13−16,23,38,41,66] and concluded that the level of evidence for a 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 hydroxychloroquine with sulfasalazine [68]. This study observed an increased risk of 30-day cardiovascular mortality (HR = 2.19, 95% CI 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 end points including mortality. However, these studies did not report all the published and unpublished literature, including a very limited number of studies: from three articles [19,20] to six articles [21]. These previous meta-analyses did not perform subgroup and sensitivity analyses to test the effect of pooling RCT and observational studies, nor did they study the source of heterogeneity. They used unadjusted risk ratios (calculated with the number of events in each group) whereas in our meta-analysis, we used adjusted relative risk [69] and we ran sensitivity analyses on the adjustment of effect size. Statistical adjustments for key prognostic variables limit confusion bias, especially in observational studies, which are not randomized. This meta-analysis confirmed the partial preliminary results of these other meta-analyses about the absence of effect for hydroxychloroquine on survival and found an increased mortality with the

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 the ISARIC WHO CCP-UK cohort

Outcome: All-cause mortality	Number of studies	Pooled relative risk (95% CI)	Risk difference (95% CI)
Hydroxychloroquine alone			
All studies	17	0.83 (0.65−1.06)	-4.4% (−9% to +1.5%)
Non-randomized studies	14	0.79 (0.60−1.04)	-5.5% (−10% to +1%)
Randomized studies	3	1.09 (0.97−1.24)	+2.3% (−0.8% to +6.2%)
Hydroxychloroquine with azithromycin			
All studies	7	1.27 (1.04−1.54)	+7% (+1% to +14%)
Non-randomized studies	6	1.29 (1.06−1.58)	+7.5% (+1.6% to +15%)
Randomized studies	1	0.64 (0.18−2.24)	-9% (−21% to +32%)

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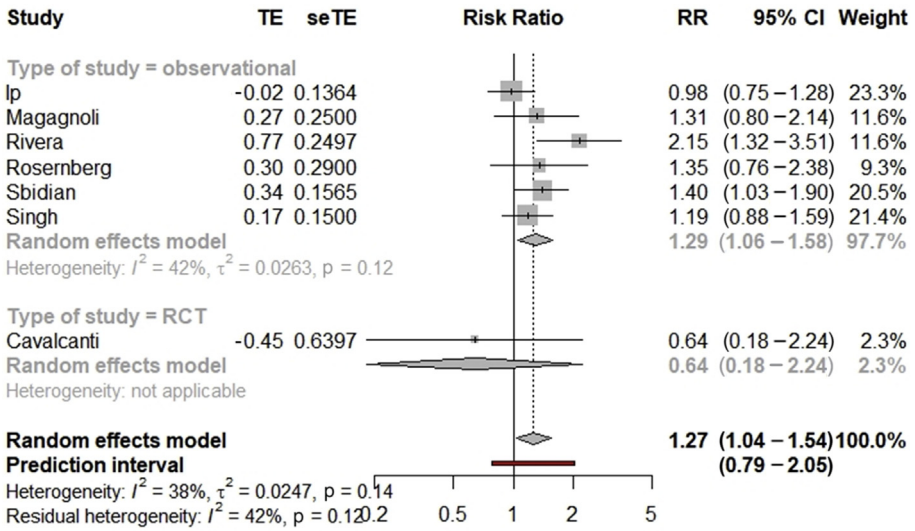

Fig. 3. Forest plot of the association between hydroxychloroquine with azithromycin and COVID-19 mortality (excluding studies with critical risk of bias). RR, risk ratio.

use of the combination of hydroxychloroquine with azithromycin 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 individuals treated with this combination, 6 out of 18 (33%) developed a significant increase in the QTc interval [70]. Another work found that in 84 patients treated with hydroxychloroquine + azithromycin, nine had a severe prolongation of QTc [71]. The combination of hydroxychloroquine + azithromycin was associated with a greater variation in the QTc interval compared with hydroxychloroquine alone in a study with 90 patients [72]. 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 [73]. The combination of the two drugs posed an even greater risk of life-threatening acute cardiac effects [18,72,73].

Several national health organizations (US Food and Drug Administration [74], French Agency for the Safety of Health Products [75], European Medicine Agency [76]) raised concerns about using unapproved drugs for COVID-19. The French Agency for the Safety of Health Products and the US Food and Drug Administration removed the authorization for the use of hydroxychloroquine outside clinical trials. The Indian Council of Medical Research took the opposite position and recommended chemoprophylaxis with hydroxychloroquine for asymptomatic individuals [77]. Finally, in the comparative peer-reviewed studies, a clear conclusion on hydroxychloroquine is not possible because of the small sample size, the lack of well-performed RCT (mainly non-randomized and retrospective studies) and inconsistent results. Many preprints without a comparative group and without randomization added to confusion surrounding this highly politicized topic [78]. There is a gap between the speed of clinical research and the expectation of a clear solution to treat people with COVID-19. Indeed, producing robust clinical trials is necessarily time-consuming. In a press communication, on 20 June 2020, the US National Institutes of Health stopped the clinical trial of hydroxychloroquine because this drug was very unlikely to be efficient for treatment of individuals with COVID-19 [79]. Based on SOLIDARITY trial results, the WHO previously took the same decision [80].

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 (versus 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% [81]. There is limited evidence to identify whether grey studies have a poorer methodological quality than published studies [82].

A major limitation is the inclusion of individuals with different levels of COVID-19 severity. However, we could not conduct subgroup analysis for severity because most study 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 hydroxychloroquine (dosing, timing between hospital administration and intervention, duration). In some studies, these data were not reported at all. Another limitation comes from the studies that did not report adjusted effect size when mortality was not the primary end point, 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 studies, 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, which are not yet published or communicated [80].

In conclusion, this meta-analysis clearly shows that hydroxychloroquine alone is not effective for the treatment of people with COVID-19 and that the combination of hydroxychloroquine and azithromycin increases the risk of mortality. These data support current clinical recommendations such as those of the National Institutes of Health [83], which do not recommend the use of hydroxychloroquine alone or in combination with azithromycin for COVID-19. There is already a great number of studies that have evaluated hydroxychloroquine alone or in combination [10] and it

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seems unlikely at this stage that any efficacy will 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 [80,84].

Transparency declaration

All authors declare no support from any organization for the submitted work other than that described above; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

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Authors' contributions

TF designed the research. TF, MR, AG, MM, NPS and YMS conducted the research. TF performed the statistical analysis and 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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Appendix A. Supplementary data

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