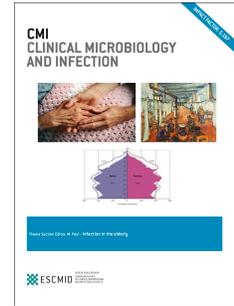


# Journal Pre-proof

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

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

4

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**58 Abstract****59 Background**

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

**62 Objective**

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

**66 Data sources**

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

**69 Study eligibility criteria**

70 We included published and unpublished studies comparing the mortality rate between patients treated  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

**73 Participants**

74 Patients  $\geq 18$  years old with confirmed COVID-19

**75 Interventions**

76 Chloroquine or hydroxychloroquine with or without azithromycin

**77 Methods**

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

**80 Results**

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

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

## 92 **Conclusion**

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

96  
97  
98  
99  
100 **Abbreviations:** HCQ: Hydroxychloroquine; AZI: Azithromycin; CI: Confidence Interval; RR:  
101 Relative Risk; HR: Hazard Ratio, OR: Odds Ratio; RCT: Randomized Controlled Trial; US FDA: US  
102 Food and Drug Administration; EMA: European Medicine Agency

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**113 Introduction**

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

124

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

129

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

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

**140 Methods**

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

**144 PICO question:**

145 **Population:** patients with confirmed COVID-19

146 **Intervention:** HCQ or CQ, with or without AZI

147 **Comparison:** a standard of care

148 **Outcomes:** the survival rate of COVID-19 patients

**149 Data sources, search strategy**

150 A search was performed using PubMed, Web of Science, Embase and Cochrane Review up to July 25,  
151 2020 with the following string search: (COVID-19 OR SARS-CoV-2) AND (MORTALITY OR  
152 DEATH) AND (HYDROXYCHLOROQUINE OR HCQ) (Supplementary text S1). Given that the  
153 number of articles about HCQ and COVID-19 is rapidly growing, we also manually searched for  
154 additional references on the MedRxiv preprint server and on Google Scholar with the same terms. An  
155 additional search on PubMed, Web of Science and Cochrane Review was conducted for chloroquine  
156 with the search terms described in Supplementary materials S1: (COVID-19 OR SARS-CoV-2) AND  
157 (MORTALITY OR DEATH) AND (CHLOROQUINE OR CQ). This meta-analysis was conducted  
158 following PRISMA statements in Supplementary text S2. This study has been recorded on the  
159 international database of prospectively registered systematic reviews, PROSPERO (Registration  
160 number: CRD42020190801).

**161 Study selection:**

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

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

169

#### 170 **Data extraction**

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

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

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

#### 182 **Individual risk of bias**

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

#### 185 **Outcome**

186 The outcome was the mortality of COVID-19 patients.

187

#### 188 **Statistical analysis**

##### 189 **Effect of CQ/HCQ alone and HCQ + AZI**

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

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

198  
199 Heterogeneity was assessed by the Cochrane Q test and  $I^2$  test [30].  $30\% < I^2 < 60\%$  was interpreted as  
200 moderate heterogeneity and  $I^2 > 60$  as substantial heterogeneity. A funnel plot was constructed to assess  
201 the publication bias. Begg's and Egger's tests were conducted to assess the publication bias [31,32].  
202 RR or HR were used to assessed mortality risk within a 95% confidence interval. In the main analysis,  
203 studies with critical bias were excluded. A sensitivity analysis including these studies, was conducted.  
204 A Bayesian meta-analysis was performed to test the robustness of our results, allowing incorporation  
205 of full uncertainty in all parameters [33]. The traditional random-effect model has fixed parameters for  
206 the distribution of the true treatment effect RR with an unknown mean  $\theta$ , within-study variance  $\sigma^2$  and  
207 between study variance  $\tau^2$ . The Bayesian random-effect model assumes these parameters are random  
208 with a probability distribution. Two prior distributions were tested  $\mu \sim \text{Normal}(1, 100)$  with a large  
209 variance and  $\tau \sim \text{Half-Cauchy}(0, 0.5)$  and a second scenario with  $\mu \sim \text{Normal}(1, 1)$  and  $\tau \sim \text{Half-Cauchy}$   
210  $(0, 0.5)$ . The Bayesian analysis was conducted with the R package "brms" [34].

211

### 212 **Subgroup analysis**

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

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

223

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

## 226 **Results**

### 227 **Literature Search**

228 A flow chart is presented in Figure 1. After searching Pubmed, Cochrane Review and Web of Science,  
229 839 articles were identified. After screening the title and the abstract, only 21 articles about  
230 hydroxychloroquine and COVID-19 were included for further consideration. We excluded 564 articles  
231 that did not meet the inclusion criteria. We did not find any non-English articles meeting our inclusion  
232 criteria. Two duplicate studies on the same cohort were excluded [12,36]. Two Chinese randomised  
233 controlled trials on hydroxychloroquine reported zero deaths in both treatment and control groups  
234 [37,38] and thus their results were not included in our meta-analysis. Ten articles from  
235 Medrxiv/Google Scholar were added. Thus, 29 articles were included, of which 25 were observational  
236 studies, one was an interventional non-randomized study and three were randomized controlled trials  
237 (RCT). These studies included 27 articles for HCQ [14–19,23,24,36,39–56] and 12 articles for  
238 HCQ+AZI [18,36,41,42,47,48,50,51,57–60]. For CQ, after searching Pubmed, Cochrane Review,  
239 Embase and Web of Science, 449 articles were identified. After screening the title and the abstract,  
240 only 1 Brazilian RCT and 3 observational studies studied chloroquine and COVID-19. However,  
241 among these studies, Gabriela Silva Borba et al. and Saleh et al. studies did not have a standard of care  
242 comparative group [61,62]. Khamis et al. did not report death data related to chloroquine and Huang  
243 et al. did not report any death [63,64]. Consequently, no study on chloroquine met our inclusion  
244 criteria.

245

### 246 **Study characteristics**

247 This meta-analysis included 15,190 patients in the HCQ group, 8081 patients in the HCQ with AZI  
248 and 14,060 patients in the standard of care group with 3,152 deaths, 1,063 deaths and 2,857 deaths,  
249 respectively. Individual studies are described in Tables S1 and S2. All included studies except one  
250 (Skipper et al.) were carried out on hospitalized patients [39]. Mean ( $\pm$  SD) age of participants was  
251  $62.1 \pm 8.5$  years. Ten studies were conducted in the USA [15,18,23,41,42,49,50,53,56,58], 4 in Spain  
252 [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  
253 China [14], one in Brazil [51] and three in several other countries (USA, Canada, Italy and  
254 Spain)[39,47,52]. Twenty-two articles were published [13–15,17,18,24,39,41,43,44,46,49–  
255 54,56,57,59,60,65], and 6 articles were preprints [16,23,40,42,48,58]. Mean daily dose of HCQ ranged  
256 from 333 mg/j to 945 mg/j. Few studies precisely described concomitant use of corticosteroids (Table  
257 S3) [15–17,44,48,50–52,65]. Only the RECOVERY trial precisely reported the use of dexamethasone  
258 (8% vs 9% in both arms) [40].

259

### 260 **Study quality**

261 Risk of bias was assessed with ROBINS-I for non-randomised studies (n=26) and Rob2 for RCT (n=3)  
262 (Figures S1-S2). Three RCT had some concerns [39,40,51] and one interventional non-randomized  
263 study had critical risk of bias [24]. Among the observational studies, fifteen articles had a moderate or  
264 serious risk of bias [13–18,41,42,44,46–48,56,58] and ten studies had a critical risk of bias  
265 [23,43,49,50,52–54,59,60,65]. Eleven observational studies did not report adjusted effect sizes to  
266 control confusion and selection bias [23,24,43,44,49,53,54,57,59,60,65]. Quality of studies was  
267 lowered by the lack of information about the assignment of treatment, the time between start of  
268 follow-up and start of intervention), some unbalanced co-intervention with other antiviral and  
269 antibiotic drugs and imbalance between groups for confounders such as comorbidities and age.

270

### 271 **Hydroxychloroquine and mortality**

272 After excluding studies with critical bias, the pooled RR for COVID-19 mortality was 0.83 (95%CI:  
273 0.65-1.06, n=17 studies) indicating no significant association between HCQ and COVID-19 mortality  
274 (Figure 2). Under the hypothesis of having a baseline mortality risk of 26% (based on ISARIC WHO

275 CCP-UK cohort [29]), these pooled relative risk values would correspond to a non-significant risk  
 276 difference of -4.4% [29] (Table 1). There was a significant subgroup difference between RCT and  
 277 non-randomized studies ( $P_{\text{heterogeneity between}} = 0.03$ ) with respectively  $RR_{\text{RCT}}=1.09$  (95%CI: 0.97-1.24)  
 278 and  $RR_{\text{non-randomized}}= 0.79$  (95%CI: 0.60-1.04) (Figure 2). Among observational studies with a moderate  
 279 risk of bias, we found no association between HCQ and mortality  $RR_{\text{moderate bias}}=1.03$  (95%CI: 0.91-  
 280 1.17,  $I^2=0\%$ ,  $n=7$  studies) with no subgroup heterogeneity (Table S4, Figure S3). Results remained  
 281 nonsignificant with influence analysis (Figure S4). The Bayesian meta-analysis led to similar results  
 282 with a pooled RR for mortality of 0.93 (95%CI: 0.72-1.14,  $n=17$  studies) (Table S5, Figure S5). In  
 283 sensitivity analysis, after inclusion of studies with critical risk of bias, the global RR was marginally  
 284 not significant 0.80 (95%CI: 0.65-1.00) (Table S6).

285

Outcome: all-cause mortality	Number of studies	Pooled Relative Risk	Risk difference
<b>Hydroxychloroquine alone</b>			
<b>All studies</b>	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%]
<b>Hydroxychloroquine with azithromycin</b>			
<b>All studies</b>	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%]

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

289

290 There was a significant higher heterogeneity among non-randomised studies as compared to RCT ( $I^2$   
 291 =84%,  $P_{\text{heterogeneity within}} < 0.01$ ). In fact, heterogeneity was null for RCT. Egger's test ( $p = 0.68$ ) and  
 292 Begg's test ( $P=0.13$ ) were not significant for asymmetry of the funnel plot indicating that there was no  
 293 major publication bias for non-randomized studies (Figure S6).

294

295

296 **Hydroxychloroquine with azithromycin and mortality**

297 After exclusion of studies with critical bias, the pooled RR for COVID-19 mortality was 1.27 (95%CI:  
298 1.04-1.54, n=7) indicating an increased mortality linked to the use of hydroxychloroquine with  
299 azithromycin. With a baseline hospital mortality of 26%, we identified a significant absolute risk  
300 difference of +7%. We found an increased risk of mortality in patients treated with  
301 hydroxychloroquine and azithromycin compared to standard of care (RR: 1.29 (95%CI: 1.06-1.58,  
302 n=6)) among non-randomized studies but this relationship was not found in the single Brazilian RCT,  
303 with no heterogeneity observed across the study design ( $P_{\text{heterogeneity between}} = 0.28$ ) (Figure 3). There was  
304 a low heterogeneity across the included studies ( $I^2 = 38\%$ ,  $p=0.14$ ). Egger's test ( $p= 0.70$ ) and Begg's  
305 test ( $p=0.65$ ) were not significant but the asymmetry in the funnel plot indicates that a publication bias  
306 could be present (Figure S7). However, the number of included studies was small. Subgroup analyses  
307 are described in supplementary material (Table S4, Figure S8). The Bayesian meta-analysis led to  
308 similar results with a pooled RR for mortality of 1.32 (95%CI: 0.97-1.68, n=7 studies) (Table S5,  
309 Figure S9). The increase in mortality was also significant with influence analysis (Figure S10).

310

## 311 Discussion

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

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

324

325

326 A previous systematic review only included 8 studies on all-cause mortality in COVID-19 patients  
327 [13–16,23,38,41,66] and concluded that the level of evidence for hydroxychloroquine effect was very  
328 weak[67]. A preprint meta-analysis, using routinely collected records from clinical practice in  
329 Germany, Spain, the UK, Japan, and the USA, compared the use of HCQ with sulfasalazine [68]. This  
330 study observed an increased risk of 30-day cardiovascular mortality (HR=2.19 [1.22-3.94]), although  
331 the study lacked a standard of care comparative group. Some previous meta-analyses were also  
332 conducted on hydroxychloroquine and various health endpoints including mortality. However these  
333 studies did not report all the published and unpublished literature, including a very limited number of  
334 studies: from 3 articles[19,20] to 6 articles[21]. These previous meta-analyses did not perform  
335 subgroup and sensitivity analysis to test the effect of pooling RCT and observational study, nor did  
336 they study the source of heterogeneity. They used unadjusted risk ratio (calculated with the number of  
337 events in each group) whereas in our meta-analysis, we used adjusted relative risk [69] and we ran  
338 sensitivity analysis on the adjustment of effect size. Statistical adjustments for key prognostic  
339 variables limit confusion bias, especially in observational studies which are not randomised. This  
340 meta-analysis confirmed the partial preliminary results of these other meta-analyses about the absence  
341 of effect for HCQ on survival and found an increased mortality with the use of the combination of  
342 HCQ with AZI in COVID-19 patients. These results confirm the preliminary findings of several  
343 observational studies which have shown that the combination of hydroxychloroquine and  
344 azithromycin might increase the risk of acute, life-threatening cardiovascular events [70]. A first study  
345 found that, among patients treated with this combination, 6 out of 18 (33%) developed a significant  
346 increase in the QTc interval.[71] Another work found that in 84 patients treated with HCQ + AZI, 9  
347 had a severe prolongation of QTc [72]. The combination of HCQ + AZI was associated with a greater  
348 variation in the QTc interval compared to hydroxychloroquine alone in a study with 90 patients [73].  
349 In a study conducted in New York on 1438 patients cardiac arrest was significantly more likely in  
350 patients receiving hydroxychloroquine with azithromycin compared to patients receiving neither of the  
351 two drugs (adjusted OR, 2.13 [95% CI, 1.12-4.05]) [18]. Finally, a study conducted on the WHO

352 database bringing together more than 167,000 patients found an increased risk of potentially fatal  
353 acute cardiac events in patients treated with azithromycin alone or with hydroxychloroquine alone  
354 [74]. The combination of the two drugs posed an even greater risk of life-threatening acute cardiac  
355 effects [18,73,74].

356

357 Several national health organisations (US FDA Food and Drug Administration[75], French Agency for  
358 the Safety of Health Products ANSM [76], European Medicine Agency EMA [77]) raised concerns  
359 about using unapproved drugs for COVID-19. ANSM and US FDA removed the authorization for the  
360 use of HCQ outside of clinical trials. The Indian Council of Medical Research took the opposite  
361 position and recommended chemoprophylaxis with hydroxychloroquine for asymptomatic cases [78].  
362 Finally, in the comparative peer-reviewed studies, a clear conclusion on hydroxychloroquine is not  
363 possible due to the small sample size, the lack of well-performed randomised controlled trials (mainly  
364 non-randomised and retrospective studies) and inconsistent results. Many preprints without a  
365 comparative group and without randomization added to confusion surrounding this highly politicised  
366 topic[79]. There is a gap between the speed of clinical research and the expectation of a clear solution  
367 to treat COVID-19 patients. Indeed, producing robust clinical trials is necessarily time-consuming. In  
368 a press communication, on 20 June 2020, US National Institutes of Health (NIH) stopped the clinical  
369 trial of hydroxychloroquine since this drug was very unlikely to be efficient to treat COVID-19  
370 patients [80]. Based on SOLIDARITY trial results, WHO previously undertook the same decision  
371 [81].

372

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

379

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

394

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

404

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413

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418

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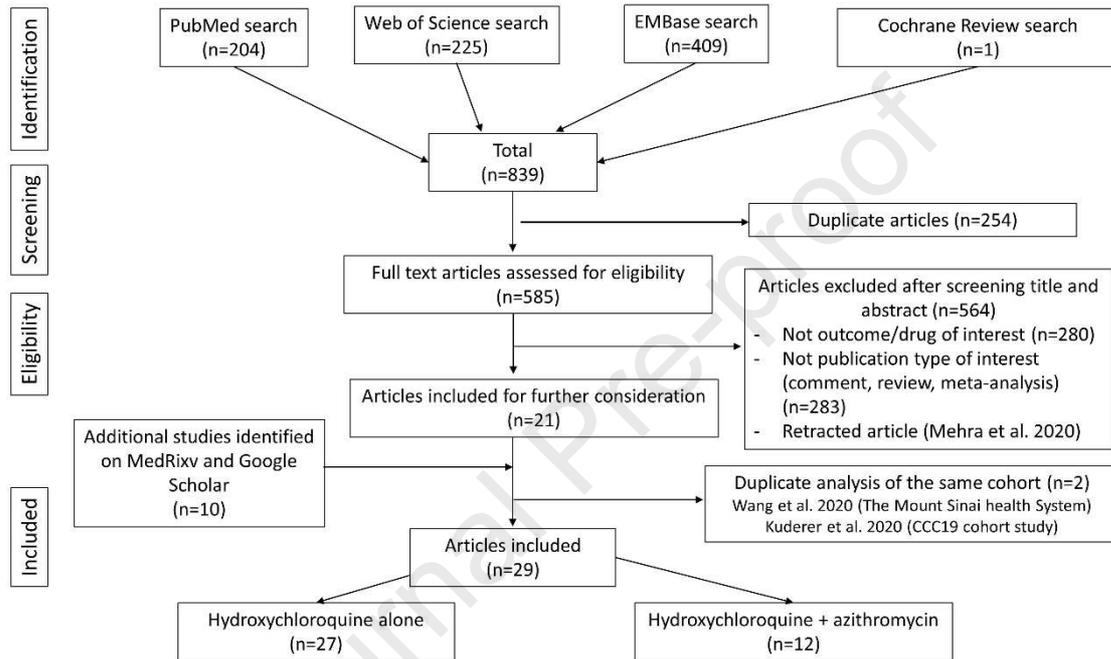


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\*Excluding studies with critical risk of bias

RR=Risk Ratio 95%-CI= 95% Confidence Interval

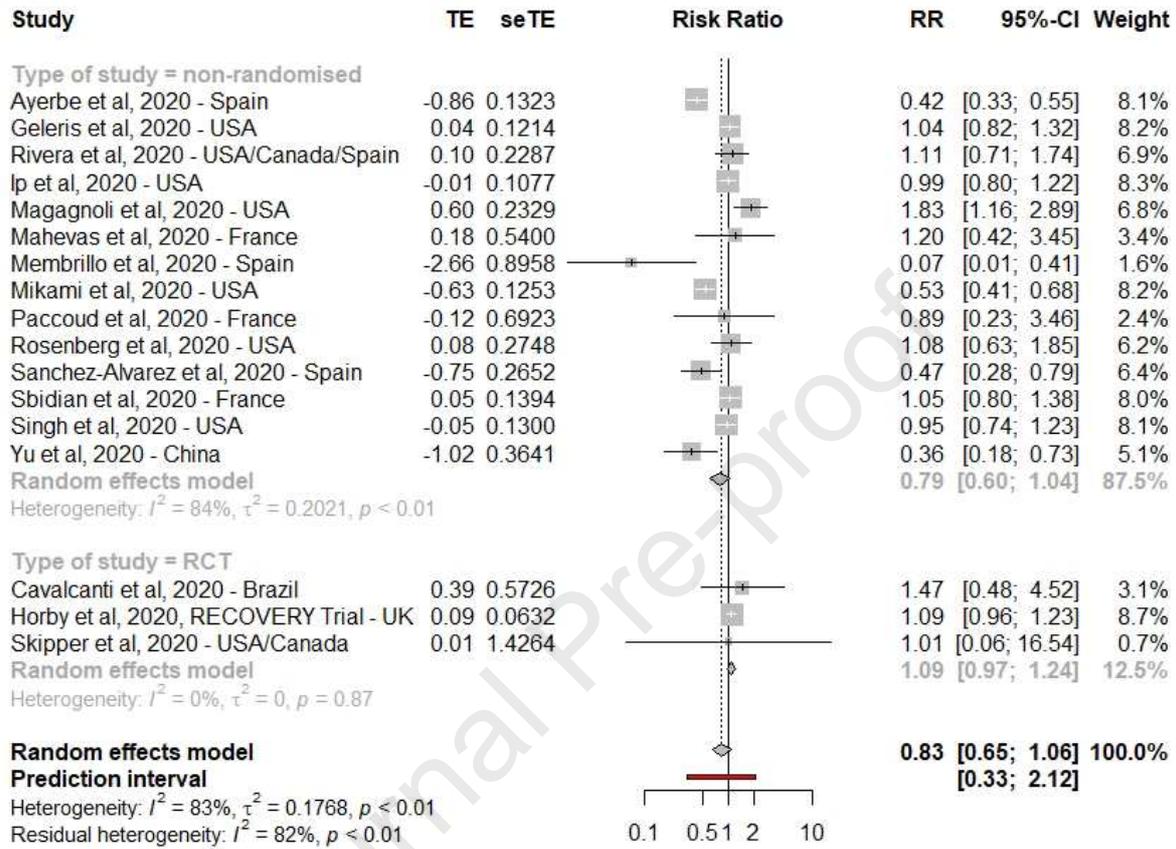


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