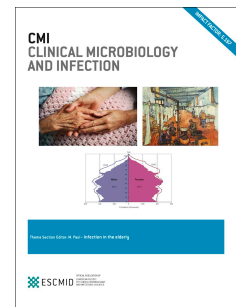# Journal Pre-proof

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

Please cite this article as: Fiolet T, Guihur A, Rebeaud M, Mulot M, Peiffer-Smadja N, Mahamat-Saleh Y, Effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients: a systematic review and meta-analysis, *Clinical Microbiology and Infection*, https://doi.org/10.1016/j.cmi.2020.08.022.

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1 CLM-20-18519.R1

2 **Title**: Effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19

3 patients: a systematic review and meta-analysis

4

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

6 Yahya Mahamat-Saleh[1, 2]

7

8 [1]CESP (Center for Research in Epidemiology and Population Health), Fac. de médecine - Univ. Paris-

9 Sud, Fac. de médecine - UVSQ, INSERM, Université Paris Saclay, 94 805, Villejuif, France

10 [2]Gustave Roussy, F-94805, Villejuif, France

11 [3]Department of Plant Molecular Biology, Faculty of Biology and Medicine, University of Lausanne,

12 Switzerland

13 [4]Laboratory of Soil Biodiversity, Faculty of Science, University of Neuchâtel, Switzerland.

14 [5]Université de Paris, IAME, INSERM, F-75018 Paris, France.

15 [6]National Institute for Health Research Health Protection Research Unit in Healthcare Associated

16 Infections and Antimicrobial Resistance, Imperial College London, London, UK.

17 [7]Infectious and Tropical Diseases Department, Bichat-Claude Bernard Hospital, AP-HP, Paris, 75018,

18 France.

19

20 **Corresponding author:**

21 *Thibault Fiolet, MSc, PhD candidate in Epidemiology

22 Center for Research in Epidemiology and Population Health

23 Inserm U1018 "Health across Generations" Team and Paris-Sud 11 University/Paris-Saclay University

24 114 rue Edouard Vaillant

25 94805 Villejuif Cedex

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

27 E-mail: Thibault.fiolet@gustaveroussy.fr

28 Twitter: @T_Fiolet

29

30   **Word count of Abstract: 313**

31   **Word count (without Abstract, Materials, References, Figures and tables): 3 451**

32   **Number of figures: 3**

33   **Number of tables:** 1

34   **Supplemental material**:

35   Supplementary Figures: 10

36   Supplementary Tables: 6

37   Supplementary Texts: 2

38   Supplementary File: 1 Excel file

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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 ≥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.

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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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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.

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 θ, within-study variance σ^2 and

207 between study variance τ^2. The Bayesian random-effect model assumes these parameters are random

208 with a probability distribution. Two prior distributions were tested $\mu \sim$ Normal (1,100) with a large

209 variance and $\tau \sim$ Half-Cauchy (0,0.5) and a second scenario with $\mu \sim$ Normal (1,1) and $\tau \sim$ 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 $RR_{unadjusted}$ vs

216 $RR_{adjusted}$), 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 included27 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**

9

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 (± SD) age of participants was

251   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

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 ROBIN-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_{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
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%]

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 ($P_{heterogeneity\ between} = 0.28$) (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 hydroxchloroquine 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

405 **Conflict of interests**: All authors declare: no support from any organisation for the submitted work

406 other than that described above; no financial relationships with any organisations that might have an

15

407   interest in the submitted work in the previous three years; no other relationships or activities that could

408   appear to have influenced the submitted work.

409

410   **Funding**: There was no specific funding for this meta-analysis.

411   **Acknowledgments**: The authors would like to thank Dominique Meroux for proofreading the

412   manuscript. We also thank Drifa Belhadi for her helpful comments on the manuscript.

413

414   **Contribution:** TF designed the research. TF, MR, AG, MM, NPS and YMS conducted the research.

415   TF did the statistical analysis. TF wrote the first draft of the paper. MR, AG, MM, NPS and YMS

416   contributed to the writing of the paper. All authors contributed to the data interpretation, revised each

417   draft for important intellectual content, and read and approved the final manuscript.

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420   **References**

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List of figures
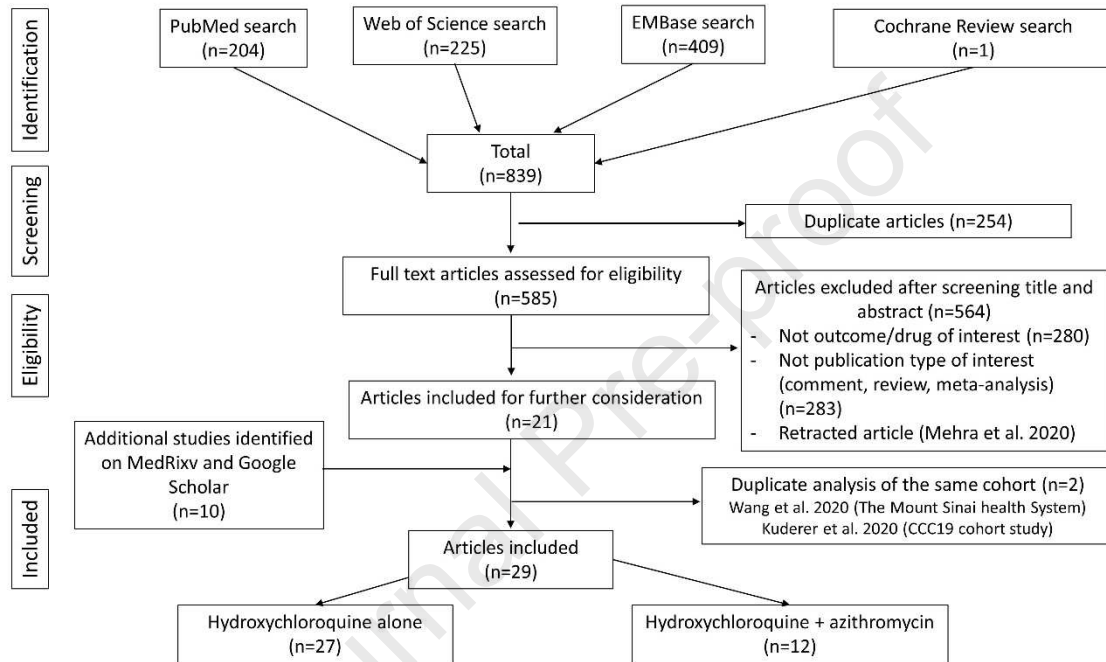
Figure 1: Flow diagram of study selection process

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

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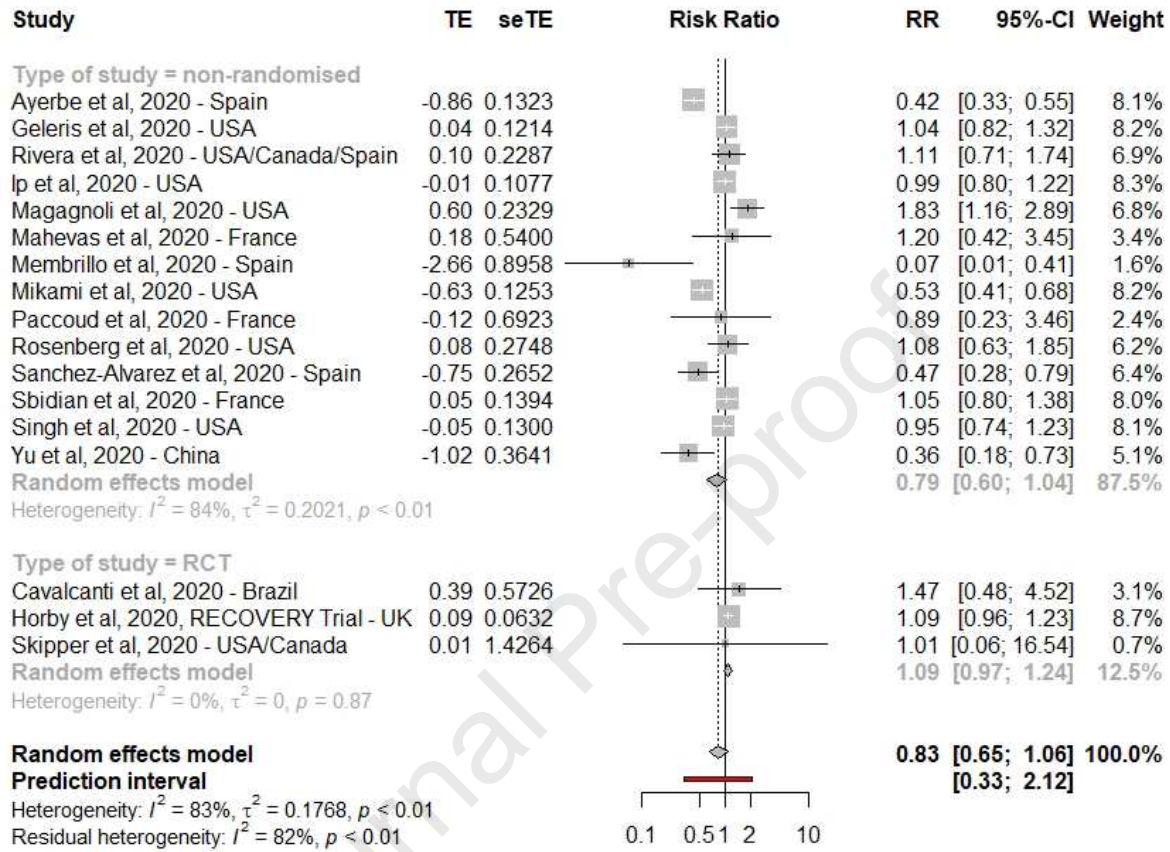RR=Risk Ratio   95%-CI= 95% Confidence Interval

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

Study	TE	seTE	Risk Ratio	RR	95%-CI	Weight
Type of study = observational						
Ip	-0.02	0.1364		0.98	[0.75; 1.28]	23.3%
Magagnoli	0.27	0.2500		1.31	[0.80; 2.14]	11.6%
Rivera	0.77	0.2497		2.15	[1.32; 3.51]	11.6%
Rosernberg	0.30	0.2900		1.35	[0.76; 2.38]	9.3%
Sbidian	0.34	0.1565		1.40	[1.03; 1.90]	20.5%
Singh	0.17	0.1500		1.19	[0.88; 1.59]	21.4%
Random effects model				1.29	[1.06; 1.58]	97.7%
Heterogeneity: $I^2 = 42\%$, $\tau^2 = 0.0263$, $p = 0.12$						
Type of study = RCT						
Cavalcanti	-0.45	0.6397		0.64	[0.18; 2.24]	2.3%
Random effects model				0.64	[0.18; 2.24]	2.3%
Heterogeneity: not applicable						
Random effects model				1.27	[1.04; 1.54]	100.0%
Prediction interval					[0.79; 2.05]	
Heterogeneity: $I^2 = 38\%$, $\tau^2 = 0.0247$, $p = 0.14$						
Residual heterogeneity: $I^2 = 42\%$, $p = 0.12$						

0.2   0.5   1   2   5