Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients: authors' response

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To the editor,

We share the concerns of Siang Know et al. about the use of azithromycin. In response to Million et al. and Lacout et al., we want to clarify some points that may have been misunderstood.

Million et al. start their letter by stating that they did not 'believe' in our study [1]. This word is inappropriate in evidence-based medicine. The authors of the letter generalize their conclusion from an observational single-centre study [2] which suffers from critical biases as summarized below:

1. Defining the exposure as "*hydroxychloroquine (HCQ) with azithromycin (AZI) ≥ 3 days*" produces an immortal time bias in favour of the HCQ-with-AZI group [3], which was not taken into account. Thus, patients with an early clinical aggravation were systematically moved to the 'other treatments' group, artificially overestimating the effect of the HCQ–AZI association. Patients who stopped the treatment before 3 days had the highest mortality rate. The immortal time bias is obvious on the Kaplan–Meier curves (Fig. 3 of Lagier et al. [2]).
2. The control group is heterogeneous: the 'other treatments' group combines patients who received HCQ alone, AZI alone, HCQ with AZI <3 days and no drug. This does not follow proper methodology.
3. There is a high imbalance between groups for age and comorbidities, factors associated with a poorer outcome. Moreover, patients with contraindications to HCQ or AZI were included in the control group, while they should have been excluded from the comparison.

As with all studies at risk of critical bias included in our systematic review, it was excluded from the main analysis. A sensitivity analysis including studies at risk of critical bias was performed, which only marginally modified our results (Supplementary Material Table S6).

Lacout et al. stated that we discarded three meaningful studies: Davido et al., Castelnuovo et al. and Catteau et al. [4–6]. This comment is not relevant since these three articles were published after the date of our systematic review, performed on the 25th of July, as is clearly reported in the abstract and in the method section.

The statement that we used 'subjective and specious' inclusion criteria is wrong. All our inclusion criteria for study selection were prespecified in PROSPERO (registration number: CRD42020190801) [7]. Our work followed the Cochrane Review methods [8], and was reported according to the PRISMA guidelines [9]. The criteria for the inclusion in the main analysis were based on the risk of bias assessment with validated tools (ROBIN-I and RoB2) [1,2,10].

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Subgroup analyses, leave-one-out-method and a Bayesian approach showed consistent results. Data and methods are publicly available. Accusations of cherry-picking are unfounded.

In comparison, flaws in the 'meta-analysis' of Million et al. are numerous [11]:

1. There is no flow chart, no clear (nor prespecified) inclusion/exclusion criteria, no risk of bias assessment using validated international Cochrane tools (to avoid 'garbage in, garbage out'), and the protocol is not pre-registered on PROSPERO.
2. In their Fig. 2, the forest plot combines different outcomes (mortality, clinical evolution, CT scan imaging) and different treatments (hydroxychloroquine alone, chloroquine alone, hydroxychloroquine with azithromycin) in the same random-effect models. Moreover, some studies appear several times in the calculation of the pooled odds ratios. This is seriously misleading.
3. Overall, Million et al. do not follow Cochrane methods and PRISMA guidelines [8,9]. Consequently, this questionable work was not mentioned in our study.

Million and Lacout et al. criticize the inclusion of Skipper et al. and the RECOVERY trial [12,13]. These trials were included since the treatment effect was similar in the clinically diagnosed and the PCR-confirmed subgroups in both studies. In the RECOVERY trial, 90% of patients were tested, and there was no difference between the analysis including all participants and the analysis restricted to the PCR-confirmed patients (HR for mortality 1.09 (0.96–1.23) and 1.09 (0.96–1.24), respectively). Additionally, the rate of PCR-confirmed patients was well balanced as expected in an RCT. Skipper et al. wrote: *"In subgroup analyses, participants with epidemiologic linkage or probable COVID-*19 by *case definition only had similar responses to those with PCR-confirmed COVID-19. PCR-confirmed cases had the least effect observed."* We also note that Million et al. surprisingly included in their systematic review an observational study, Guérin et al., with only 58% of the patients with confirmed PCR tests, and they did not conduct any sensitivity analyses [14]. The statement that the RECOVERY trial used a toxic dose comes from a misunderstanding of pharmacokinetic models on (hydroxy)chloroquine. In the RECOVERY trial, 2400 mg were used only for the first day to provide free plasma concentrations as high as safely possible and faster than when using only the maintenance dose from the start [15–17].

The statement that Rivera et al. used unreliable data—*"Participation by anonymous individual health-care practitioners"*—is misleading. The Covid-19 and Cancer Consortium (CCC19) study used anonymized data from the U.S. Census Divisions [18]. Million et al. wrote that Rivera et al. did not report results on 'HCQ + AZI' use but on 'HCQ + other medication'. This is correct. However, HCQ + AZI was the most common combination treatment. Moreover, our conclusion is unchanged when omitting Rivera et al. from pooled OR estimation (Supplementary Material Fig. S10, OR = 1.18, 95%CI 1.00–1.38). Million et al. claim that Rivera's study did not adjust on COVID-19 severity, but adjustment on baseline severity of COVID-19 and other baseline characteristics is reported in the Method section of this study. Overall, the assertions of Million et al. and Lacout et al. are not based on solid evidence.

More than 30 countries do not recommend the use of hydroxychloroquine (except in clinical trials) in their national guidelines (Supplementary Material Table S1). Two recent meta-analyses restricted to RCTs confirmed our findings [19,20]. Several RCTs for mild to moderate COVID-19 and two RCTs in prophylaxis found no benefit [12,21–23]. The will to discard solid evidence from well-conducted randomized trials, and emphasizing weak evidence from critically biased observational studies, is of no use in the search for a cure for COVID-19.

Author contributions

TF wrote the first draft of the paper. MR, AG, MM, NPS and YMS contributed to the writing of the paper. All authors revised each draft for important intellectual content and read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.10.002.

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