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

Re: effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients: author's response

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To the editor,

We would like to explain several points raised by Védrines et al.

1. We agree that Geleris et al. used a composite endpoint [1]. However, (a) intubation is a main prognostic factor for death, (b) exclusion of this study from the pooled RR estimation did not change our conclusion (see Table S4) and (c) Geleris et al. did not report adjusted hazard ratio (HR_a) for death only.

In our main analysis, we used this adjusted HR which takes into account indication bias (following the Cochrane recommendation [2]). Crude relative risk (RR) for death only may be estimated from the data reported in Geleris et al.: with 157 deaths among the hydroxychloroquine group ($n = 811$) and 75 deaths among the control group ($n = 565$), the new estimated RR is even higher: 1.45 (95% CI 1.13–1.87).

2. Magagnoli et al. used a specific Cox model adapted for length-biased data on the overall population ($n = 807$) [3,4]. The sub-analysis among patients who were admitted during the first 4 weeks of study, discussed by Védrines et al. represents half of the initial cohort: that is why we used the HR reported in their main analysis.

Using the HR from the subgroup cohort and the new HR for Geleris et al. leads to similar results with the pooled RR = 0.82 (95% CI 0.64–1.04) for hydroxychloroquine (HCQ) (Fig. S1) and RR = 1.23 (95% CI 1–1.53) for HCQ + azithromycin (AZI) (Fig. S2), indicating no benefit from HCQ with or without AZI. We thank Védrines et al. for leaving us the opportunity to illustrate again the robustness of our conclusion.

3. The point concerning Rivera et al. was already answered [5]. We note that this is the second letter from Dr Lacout, which is quite uncommon for the same study.
4. The Arshad et al. study was excluded from our main analysis because of numerous critical biases described in our supplementary materials and in two letters and one editorial [6–9].

Briefly, this study suffers from immortal time bias and residual confounding, and it is not possible to know if the observed risk reduction is due to hydroxychloroquine or corticosteroids use. Finally, Védrines et al. may be interested by the sensitivity analysis including studies at risk of critical bias, which was provided in our Table S6 [10].

5. The statement that we misrepresented four original works is fallacious.

Nevertheless, we agree with Védrines et al. on one point: even if we carefully evaluated all studies of our systematic review

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following the Cochrane Review methods, and reported all results according to PRISMA guidelines, observational studies are not the reference standard for therapeutic evaluation. Since our work was published, several other randomized controlled trials have become available. Overall, the RECOVERY trial, the SOLIDARITY trial and recent meta-analyses confirmed our conclusion [10–16]: hydroxychloroquine was not associated with a decrease in mortality for hospitalized patients. The Axfors et al. meta-analysis, based on 26 published and unpublished RCTs (including SOLIDARITY and RECOVERY trials), found a significant increased risk for mortality [14]. Thus, there is no need to reconsider our conclusion. We advise Védrines et al. to consider the last published articles and evidence. Védrines et al. stated that reality is complex. We agree, and we add that because reality is complex solid evidence of a favourable benefit–risk ratio is necessary. The COVID-19 crisis does not make the need for rigorous science obsolete: it reinforces this need.

As stated by the author of a recent editorial on studies evaluating tocilizumab, another putative treatment for COVID-19 patients, "I plan to wait out the torrent of positive observational studies and reconsider tocilizumab's use in COVID-19 if, and only if, more compelling data from randomized trials emerges." Regarding hydroxychloroquine, the torrent of positive observational studies, often of very low quality, has been shared, but compelling data from randomized trials have already been published and are univocal: hydroxychloroquine with or without azithromycin is not an effective treatment for patients with COVID-19 [17].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.10.031.

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