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' by Fiolet *et al.*

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To the Editor,

We read with interest the meta-analysis entitled "*Effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients: a systematic review and meta-analysis*" published in *Clinical Microbiology and Infection* by Fiolet *et al.* [1]. This meta-analysis concluded that the combination of hydroxychloroquine (HCQ) and azithromycin (AZ) was associated with increased mortality and that HCQ alone had no effect on mortality.

We believe that this study is flawed. To start with, its conclusion is questionable in light of the results of our observational study which compared 3119 patients treated for at least 3 days with HCQ–AZ and 618 patients undergoing other treatments; there was a reduction in mortality in the population at risk (>60 years) by a factor of two [2]. In this context, we sought to understand how the authors reached their conclusions.

First, none of the authors has extensive experience in the treatment of infectious diseases, and a generic systematic review of literature does not replace expert understanding of study methods and pitfalls, as we have described [3]. The authors report several meta-analyses but omitted ours [4]. The fatal flaw in the analysis by Fiolet *et al.* is that it used subjective and specious criteria in the decisions about which studies to include. Large valid observational studies reporting significant benefit and published during the inclusion period, and that used standard accepted methods to control for confounding factors (propensity-score matching), were not included: notably those of Arshad *et al.* in the USA ($n = 2541$), Bernaola *et al.* in Spain ($n = 1645$), and our study of 199 patient pairs in France [2].

One inclusion criterion mentioned by the authors [1] is "*cases confirmed by RT-PCR*". This, however, is in contradiction to the inclusion of Skipper *et al.*, in which "*Only 58% of participants received SARS-CoV-2 testing*", and the RECOVERY trial for which PCR confirmation was not mandatory, and furthermore in which toxic doses were used (2400 mg HCQ within the first 24 h). Fiolet *et al.* included data from the study by Rivera *et al.* which itself is fatally flawed. In that study (of cancer patients): "*Participation by anonymous individual health-care practitioners located in Argentina, Canada, the EU, the UK, and the USA is also allowed. The mechanism of data collection can be retrospective (after the course of COVID-19) or concurrent, at the discretion of the respondent.*" This is not a sampling frame for any type of epidemiological study. We cannot be sure which bias was created by this design.

Second, the data of Rivera *et al.* show dramatic differences in HCQ and AZ use for non-treated versus treated subjects by baseline disease severity, and the authors did not report results on HCQ + AZ use but on HCQ + other medication use, which is not adjusted adequately for severity. Simply put, patients with worse conditions were given more medications and were more likely to die of their cancers.

Three new retrospective studies published after the inclusion period and not included in the systematic review further contradict the authors' conclusions. The study of 8075 patients in Belgium [5], 3451 patients in Italy [6] and 890 European patients with cancer [7] report clear benefits of chloroquine derivatives on mortality. Contrary to the authors' conclusions, the careful and updated analysis

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of the literature shows that hydroxychloroquine, particularly when associated with azithromycin, remains one of the best options to date in the treatment of COVID-19 [8].

Author contributions

Writing – original draft: MM and YR. Writing – review & editing: JCL and DR. Conceptualization: DR.

Transparency declaration

The authors declare no competing interests. No funding was received. Our Marseille group used widely available generic drugs distributed by many pharmaceutical companies.

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