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

Matthieu MILLION[1,2], Yanis ROUSSEL[1,2], Jean-Christophe LAGIER[1,2], Didier RAOULT[1,2,*]

Affiliations :

[1]IHU-Méditerranée Infection, Marseille, France

[2]Aix Marseille University, IRD, AP-HM, MEPHI, Marseille, France

***Corresponding author:** Didier RAOULT, IHU - Méditerranée Infection, 19-21 boulevard Jean Moulin, 13005 Marseille, France. Tel.: +33 413 732 401, Fax: +33 413 732 402; email: Didier.Raoult@gmail.com

Key words: SARS-CoV-2; COVID-19; hydroxychloroquine; Meta-analysis

To the Editor,

We read with interest the meta-analysis published in Clinical Microbiology and Infection by Fiolet *et al*. [1] entitled "Effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients: a systematic review and meta-analysis". 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 fatally flawed. To start with, its conclusion is impossible in light of the treatment in our center of patients with HCQ-AZ, with reduction of mortality in the population at risk (>60 years) by a factor 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 understandings of study methods and pitfalls, as we have described [3]. The authors report several meta-analyses but omitted ours [4]. Our analysis highlighted a major factor of heterogeneity between studies: Rote “Big-data” studies, with complete disconnection between data analysis and clinician expertise, and clinical studies, in which the analysis is conducted by clinicians with a precise and detailed protocol. Our work notably contributed to highlighting the Lancetgate [5] and showed that Big-data studies are associated with conflicts of interest and absence of detailed treatment protocols.

The fatal flaw of the Fiolet *et al*. analysis is that it used subjective, capricious and specious criteria 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 Arshad *et al.* in the USA (n = 2,541), Bernaola *et al*. in Spain (n = 1,645), and our study of 199 patient pairs in France.

One inclusion criterion mentioned by the authors [1] is “cases confirmed by RT-PCR”. This however is in contradiction to inclusion of Skipper *et al.*, with “Only 58% of participants received SARS-CoV-2 testing” and the RECOVERY trial for which PCR confirmation was not mandatory, as well as that it used toxic doses (2400 mg HCQ within the first 24 hours). Worse, Fiolet *et al*. included data from the study by Rivera *et al*. which itself is fatally flawed. That study, of cancer patients, included “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 epidemiologic study. There is no assurance that individual practitioners didn't select patients on which to report because the patients didn't do well on antiviral therapies. Haphazard subject collection is not a representative epidemiologic sampling method and has no justification for use. Second, the Rivera *et al*. data show dramatic differences in HCQ and AZ use for nontreated vs 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. Third, Fiolet *et al*. use results values in their forest plot that do not appear in the paper or supplement of Rivera *et al*.

Two new retrospective studies further contradict the authors' conclusions. The study of 8,075 patients in Belgium (Catteau, 2020) and 3,451 patients in Italy (Di Castelnuovo, 2020) report clear benefits of chloroquine derivatives on mortality (Figure). In this context, we present (Figure) an update of our meta-analysis [4]. The clinical studies include 4,121 patients from 7 countries, with summary odds ratio 0.60, 95% confidence interval 0.50-0.73, $p=10^{-7}$). Results were consistent among studies ($I^2=20\%$, $p=0.23$). Among the 35,985 patients included in the

Big data studies, a significant but smaller benefit was found (0.84, 0.75-0.94, p=.003) with appreciable heterogeneity (I^2=76%, p<.001).

History and reasoning demonstrates that the authors' conclusions are erroneous. We suggest that the authors leave their political motivations at the door before undertaking scientific work.

Acknowledgements

We thank Dr Harvey Risch for his contribution to the preparation of this response.

Funding

None

Declaration of competing interest

The authors declare no competing interests. Funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Our Marseille group used widely available generic drugs distributed by many pharmaceutical companies.

References

1. Fiolet T, Guihur A, Rebeaud M, Mulot M, Peiffer-Smadja N, Mahamat-SalehY. Effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients:a systematic review and meta-analysis. Clin Microbiol Infect 2020. Epub ahead of print. https://doi.org/10.1016/j.cmi.2020.08.022
2. Lagier JC, Million M, Gautret P, et al. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis. Travel Med Infect Dis 2020;36:101791. https://doi.org/10.1016/j.tmaid.2020.101791
3. Raoult D. Chronic Q fever: expert opinion versus literature analysis and consensus. J Infect. 2012;65(2):102-108. doi:10.1016/j.jinf.2012.04.006
4. Million M, Gautret P, Colson P, Roussel Y, Dubourg G, Chabrière E, et al. Clinical Efficacy of Chloroquine derivatives in COVID-19 Infection: Comparative meta-analysis between the Big data and the real world. New Microbes New Infect. Available online 6 June 2020, 100709. https://doi.org/10.1016/j.nmni.2020.100709
5. Mehra MR, Ruschitzka F, Patel AN. Retraction-Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis [retraction of: Lancet. 2020 May 22;:]. Lancet. 2020;395(10240):1820. https://doi.org/10.1016/S0140-6736(20)31324-6

Figure legend

Figure. Meta-analysis on hydroxychloroquine for COVID-19 mortality (August 26, 2020)

A. Studies published online during the inclusion period of Fiolet *et al*. [1] (before July, 25) but not included in their work are in red. Arshad, Lagier and Bernaola used propensity score matching (PSM). *Studies published after July 25, 2020. CI: confidence interval, HCQ: hydroxychloroquine, RCT: randomized controlled trial. This meta-analysis was performed with a random-effects model using Comprehensive Meta-Analysis v3 (Biostat, Englewood, NJ, USA). B. Studies included in Fiolet *et al*. [1] but excluded in the present analysis and reasons for exclusion. aOR: adjusted Odds ratio.