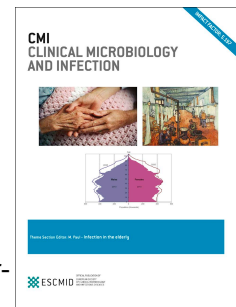# Journal Pre-proof

'Effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients' – Author's reply

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Please cite this article as: Fiolet T, Guihur A, Rebeaud ME, Mulot M, Peiffer-Smadja N, Mahamat-Saleh Y, 'Effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients' – Author's reply, *Clinical Microbiology and Infection*, https://doi.org/10.1016/j.cmi.2020.10.002.

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1 **'Effect of hydroxychloroquine with or without azithromycin on the**

2 **mortality of COVID-19 patients' – Author's reply**

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27 **Words count**: 979

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30 To the editor,

31 We share the concerns of Siang Know *et al.* about the use of azithromycin. In response to

32 Million *et al.* and Lacout *et al.,* we want to clarify some points that may have been

33 misunderstood.

34 Million *et al.* start their letter by stating that they did not "believe" in our study [1]. This word is

35 inappropriate in evidence-based medicine. The authors of the letter generalize their

36 conclusion from an observational single-center study [2] which suffers from critical biases

37 summarized below:

38 1) Defining the exposure as « Hydroxychloroquine (HCQ) with azithromycin(AZI) $\geq$ 3 days »

39 produces an immortal time bias in favor of the HCQ with AZI group [3], which was not taken

40 into account. Thus, patients with an early clinical aggravation were systematically moved to

41 the "Other treatments" group, artificially overestimating the effect of the HCQ-AZI

42 association. Patients who stopped the treatment before 3 days had the highest mortality

43 rate. The immortal time bias is obvious on the Kaplan-Meier curves (figure 3 of Lagier *et al.*).

44   2) The control group is heterogeneous: the "Other treatments" group combines patients who

45   received HCQ alone, AZI alone, HCQ with AZI <3 days and no drug. This does not follow

46   proper methodology.

47   3) There is a high imbalance between groups for age and comorbidities, factors associated

48   with a poorer outcome. Moreover, patients with contraindications to HCQ or AZI were

49   included in the control group, while they should have been excluded from the comparison.

50   As with all studies at risk of critical bias included in our systematic review, it was excluded

51   from the main analysis. A sensitivity analysis including studies at risk of critical bias was

52   performed, which only marginally modified our results (Supplementary table S6).

53   Lacout *et al.* stated that we discarded three meaningful studies: Davido *et al.*, Castelnuovo

54   *et al.* and Catteau *et al.* [4–6]. This comment is not relevant since these three articles were

55   published after the date of our systematic review, performed the 25th of July, as is clearly

56   reported in the abstract and in the method section.

57   The statement that we used "subjective and specious" inclusion criteria is wrong. All our

58   inclusion criteria for study selection were prespecified in PROSPERO (registration number :

59   CRD42020190801) [7]. Our work followed the Cochrane Review methods [8], and was

60   reported according to the PRISMA guidelines [9]. The criteria for the inclusion in the main

61   analysis were based on the risk of bias assessment with validated tools (ROBIN-I and RoB2)

62   [1,2,10]. Subgroup analyses, leave-One-Out-method and Bayesian approach showed

63   consistent results. Data and methods are publicly available. Accusations of cherry-picking

64   are unfounded.

65   In comparison, flaws in Million's "meta-analysis" are numerous [11].

66   1) There is no flow chart, no clear (nor prespecified) inclusion/exclusion criteria, no risk of

67   bias assessment using validated international Cochrane tools (to avoid "garbage in, garbage

68   out"), and the protocol is not pre-registered on PROSPERO

69　2) In their Figure 2, the forest plot combines different outcomes (mortality, clinical evolution,

70　CT scan imaging) and different treatment (hydroxychloroquine alone, chloroquine alone,

71　hydroxychloroquine with azithromycin) in the same random-effect models. Moreover, some

72　studies appear several times in the calculation of the pooled Odds Ratios. This is seriously

73　misleading.

74　3) Overall, Million *et al.* do not follow Cochrane methods and PRISMA guidelines [8,9].

75　Consequently, this questionable work was not mentioned in our study.

76　Million and Lacout *et al.* criticize the inclusion of Skipper *et al. and the RECOVERY Trial* [12]

77　[13]. These trials were included since treatment effect was similar in the clinically diagnosed

78　and the PCR-confirmed subgroups, in both studies. In RECOVERY trial, 90% of patients

79　were tested, and there was no difference between the analysis including all participants vs

80　the analysis restricted to the PCR-confirmed patients (HR for mortality: 1.09 [0.96-1.23] and

81　1.09 [0.96-1.24], respectively)　Additionally, the rate of PCR-confirmed patients was well

82　balanced as expected in a RCT.　Skipper *et al.* wrote "In subgroup analyses, participants

83　with epidemiologic linkage or probable COVID-19 by case definition only had similar

84　responses to those with PCR-confirmed COVID-19. PCR-confirmed cases had the least

85　effect observed." We also note that Million et al. to surprisingly included in their systematic

86　review an observational study, Guérin *et al.* with only 58% of the patients with confirmed

87　PCR tests and they did not conduct any sensitivity analyses [14]. The statement that the

88　RECOVERY Trial used a toxic dose comes from a misunderstanding of pharmacokinetic

89　models on (hydroxyl)chloroquine. In the RECOVERY Trial, 2400mg were only used for the

90　first day to provide free plasma concentrations as high as safely possible and faster than

91　when using only the maintenance dose from the start [15–17].

92　The statement that Rivera *et al.* used unreliable data ("Participation by anonymous individual

93　health-care practitioners") is misleading. The Covid-19 and Cancer Consortium (CCC19)

94　study used anonymized data from the U.S. Census Divisions [18]. Million et al. wrote that

95   Rivera et al. did not report results on "HCQ+ AZI" use but on "HCQ + other medication". This

96   is correct. However, HCQ+AZI was the most common combination treatment. Moreover, our

97   conclusion is unchanged when omitting Rivera et al. from pooled OR estimation

98   (Supplementary Figure S10, OR=1.18 CI95%: 1.00-1.38). Million *et al.* claim Rivera's study

99   did not adjust on COVID-19 severity, but adjustment on baseline severity of COVID-19 and

100   other baseline characteristics is reported in the Method section of this study. Overall, the

101   assertions of Million et al. and Lacout et al. are not based on solid evidence.

102   More than 30 countries do not recommend the use of hydroxychloroquine (except in clinical

103   trials) in their national guidelines (Supplementary Table S1). Two recent meta-analyses

104   restricted to RCTs confirmed our findings [19,20]. Several RCTs for mild to moderate

105   COVID-19 and two RCTs in prophylaxis found no benefit [12,21–23]. The will to discard solid

106   evidence from well conducted randomized trial, and emphasizing weak evidence from

107   critically biased observational studies, is of no use in the search for a cure against COVID-

108   19.

116   **Contribution**: TF wrote the first draft of the paper. MR, AG, MM, NPS and YMS contributed

117   to the writing of the paper. All authors revised each draft for important intellectual content

118   and read and approved the final manuscript.

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