Letter to Editor

Response to: Efficacy and safety of hydroxychloroquine/chloroquine against SARS-CoV-2 infection: A systematic review and meta-analysis

We read with interest the recent meta-analysis published in this journal by Kumar et al. [1] about the efficacy and safety of hydroxychloroquine (HCQ) in patients affected by coronavirus disease 2019 (COVID-19). Included studies in the final analysis for therapeutic effect of HCQ were 14, with 10 randomized controlled trials, and 4 non-randomized prospective cohort studies. The conclusions of this analysis reported no evidence of mortality increase for patients treated with HCQ in comparison to the control group in the non-randomized studies, while a RR = 1.10 was reported in hospitalized patients. However the Authors reported in the Supplementary Table 3 the subgroup analysis by "mild/moderate disease", but in the method section was not defined if this classification was made by clinical or other laboratory parameters; it's reasonable that the severity criteria were different among the included studies, and the dichotomous analysis "mild/moderate" could be arbitrary; in our opinion this analysis should be more correctly performed by a meta-regression using the P/F values at the admission as independent moderator for severity; the Authors reported themselves in the "Results" section that in the majority of cases HCQ was given in patients with severe disease; moreover, the HCQ dose and treatment duration were not analyzed as moderator in the subgroup analysis: this aspect represents in our opinion a serious lack in this meta-analysis because an hypothetical side-effect of HCQ should be demonstrated by a meta-regression analysis, where the risk of toxicity should be related to the increase of dose measured by a continuous values. The same objection could be proposed for the age of enrolled subjects, the treatment duration time (days) with HCQ, presence of comorbidities such as QT prolongation or other known or detected arrhythmias. It seems really unexpected that in two important and different studies as the RCT by Cavalcanti et al. [2] and the retrospective study by Million et al. [3] no significant adverse events or mortality risk were associated with the HCQ + azithromycin combination. Furthermore, another important study was excluded from this meta-analysis and is focused on the role of low-dose of HCQ (2400 mg administered in 5 days) during the COVID-19 disease with a significant higher mortality in the patients not treated with HCQ, despite an early time to admission in the hospital [4]. Considering the large amount of available data about the safety of HCQ at the standard dose in other well known

illness as malaria or rheumatic diseases, it is to be assumed that higher doses of HCQ (>2.4g during the 5 days) can lead to toxicity also due to the longer detectable plasmatic level of this drug (>50 days). The main limitation of this meta-analysis was the lack of sub-group analysis according to different HCQ dose and treatment duration; this is a crucial aspect in our opinion, because elderly patients with some comorbidities have a major risk of acute heart failure, ischemia and arrythmia in COVID-19 [5]. For this reason, the analysis of the treatment duration and the overall dose of HCQ is essential to understand the real proarrhythmic role without QTc prolongation or in presence of other COVID-19 related myocardial injury.

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None.

Declaration of competing interest

The authors declare no conflicts of interest.

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