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Letter to the Editor

Reply to "The perceived efficacy of hydroxychloroquine in observational studies: the results of the confounding effects of 'goals of care'"

Editor: Dr Jim Gray

We thank Tleyjeh and Tlayjeh for their letter [1] regarding our analysis of in-hospital mortality during the first wave of the coronavirus disease 2019 (COVID-19) pandemic and the impact of low-dose hydroxychloroquine (HCQ) therapy [2].

The authors raise various points about our study: (1) the potential impact of 'confounding by unmeasured goals of care'; (2) the need for a comprehensive competing risk analysis in the absence of follow-up data on death beyond hospital discharge; and (3) the absence of antiviral activity of low-dose HCQ.

Regarding the impact of indication bias related to limitations of care, such as do-not-resuscitate orders, this point was raised by De Schryver et al. [3] in a previous letter to the editor [3] to which we responded [4]. Briefly, another study assessing the risk factors for mortality in patients admitted to intensive care units in Belgium during the first wave of the COVID-19 pandemic found an association between the use of HCQ and decreased mortality, including inpatients on mechanical ventilation (i.e. a subcohort without any formal 'do-not-escalate' orders) [5]. The authors referred to guidelines for triaging patients based on the short-term chance of survival. One of the tools used in Belgium was the Walter Prognostic Index [6]. This involves several variables that were entered in our model (i.e. age, male sex, cardiac disease, kidney function and cancer) and some that were not available (i.e. dependency, a concept related to frailty).

For the competing risk analysis, we calculated cause-specific hazards (using the corresponding Cox model) for both competing events, and hence also for hospital discharge. No meaningful difference in size or significance emerged for the latter (the estimated adjusted effect size was cause-specific proportional hazard (cs-PH) of 0.97, with P=0.57 after adjusting for similar covariates to those corrected for in the cs-PH of death analysis). We then reported the cause-specific hazard ratio for in-hospital deaths, as did prior studies, including cumulative incidence curves for COVID-19-specific deaths, integrating both types of cs-PH (Fig. 3 of our original study [2]). The accompanying Fine and Gray analysis gave similar results.

We fully agree that HCQ, at any dose, is unlikely to have antiviral activity, as reported in various animal models and humans [7,8]. It is now widely acknowledged that the prognosis for patients with COVID-19 is driven by the host inflammatory response, which is associated with clinical deterioration, respiratory failure and diffuse thrombotic complications [4,9,10]. HCQ is a drug with well-documented anti-inflammatory and antithrombotic properties, including modulation of platelet activity; this supports the biological plausibility of benefit in patients with COVID-19 [11–14].

In conclusion, we agree that one should use due vigilance and care in analysing and interpreting observational data. We believe we followed that rule when studying the observational data available on low-dose HCQ during the first wave of the COVID-19 pandemic. Unlike studies published earlier on this topic [15], we accounted for immortal time bias through trial emulation to the extent possible, and analysed the competing risk outcomes. We further pointed to the hypothesis-generating nature of our causal effect examination due to inherent limitations of the observational study. We wish to thank the authors and the journal for giving us the opportunity to underline the importance of this, and engage in thoughtful peer discussions.

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