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Letter to the Editor

Hydroxychloroquine in COVID-19: Taking care of statistics to take care of patients

Dear Editor,

I read with great interest the article published by Arshad and the Henry Ford COVID-19 Task Force. They evaluated the role of hydroxychloroquine (HCQ) therapy alone and in combination with azithromycin in hospitalized COVID-19 patients. They included a total of 2.541 patients divided into four groups: HCQ alone, HCQ + azithromycin, azithromycin alone, and neither drug. The authors performed propensity score matching to control for confounding factors, using the parameters included in the Cox regression model. They observed the lowest mortality in the 'HCQ alone' group compared to the HCQ + azithromycin, azithromycin alone, and neither drug groups (Arshad et al., 2020).

However, some other aspects should be considered. Firstly, patients with severe COVID-19 and minimal cardiac risk factors were selected to be included in the HCQ + azithromycin group. This criterion probably conferred an *a priori* selection bias, making problematic the further correction during statistical analysis. Moreover, the median age (an important and well-known risk factor) was lowest in the HCQ alone group.

Secondly, the authors adopted mSOFA score and O_2 saturation on admission, as prognostic factors. However, 25% of the population did not have an mSOFA score available, contributing to increased potential bias. As well, mSOFA comparison raised a serious concern about bias in this study since the mSOFA mean was significantly lower in the 'HCQ alone' than in other groups. This point could probably be corrected by propensity matching. However, it is well known that validation of propensity matching depends on the variables included in the model. It is recommended to include all important and relevant variables to the outcome searched (Imai et al., 2008). However, the authors did not include mSOFA in the propensity-matching model to evaluate survival, an important and recognized prognostic score in ICU hospitalized patients. It would be of interest if authors could provide a revised analysis with mSOFA included in the propensity score match.

Finally, corticosteroids were administered more to 'HCQ alone' patients (78.9%), with a statistical difference (p-value < 0.001) than in other groups (35.7%, 38.8%, 74.3%; neither drug, azithromycin alone and HCQ + azithromycin, respectively). Recent evidence demonstrated a beneficial effect in steroid administration in COVID-19 patients, reducing mortality (Horby et al., 2020; Mahase, 2020). Considering this, would the authors' findings, indeed, represent a consequence of corticosteroids administration?

The COVID-19 pandemic promoted an increase in the number of studies in a considerably short time. However, a race to a 'silver bullet' must not compromise the science nor evidence-based medicine.

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