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A Sound Approach: Hydroxychloroquine Reduces Mortality in Severe COVID-19

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Letter to the Editor

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To the Editor:

In response:

We thank those submitting letters. It is important to critically review COVID-19 experience in a peer-reviewed, non-politicized process, and we fully support appropriately powered double-blind, randomized trials to address questions on COVID-19 clinical management. Many letters discussed several similar points, which we will address jointly. Corticosteroids (MPD) were controlled for in the multivariate and propensity analyses as were age and comorbidities, including cardiac disease and severity of illness. Age was an independent risk factor associated with mortality. We do feel that steroids have a role in reducing mortality for COVID-19 and were first to publish this (Fadel et al., 2020), however in this study, HCQ was independently associated with decreased mortality, a distinct benefit from the steroid effect. We agree with Wiseman that prospective evaluation of a stage-and-age-nuanced approach to COVID-19 that exploits the multiple mechanisms of HCQ and synergy with MPD is needed. In response to Malviya, we reported 91% of all patients began treatment within two days of admission. We agree that early therapy is of most benefit; however, we do not have information on the duration of symptoms prior to hospitalization. The mSOFA has been validated in other studies (de Grooth et al., 2017; Grissom et al., 2010); moreover, we also used hypoxia as an independent marker of disease severity. In response to Thornton, HCQ was used throughout the study period, limiting time bias. We used dosages that followed FDA guidelines, with monitoring for cardiac arrhythmias. All centers used the same treatment guideline minimizing treatment bias. The protocol we used was previously published (Fadel et al., 2020). In response to Atkinson, patients assigned to the HCQ group had a moderate and severe illness at presentation, which would favor worse outcomes with HCQ. The exclusion of patients with premorbid risk for cardiac toxicity is similar to clinical trials of many other drugs such as remdesivir, where individuals with severe liver or kidney disease were excluded (Clinical Trial, 2020).

Importantly, in response to Rosenberg, our study differed from other studies, including randomized controlled trials (RCTs), in a variety of ways, including the number of patients, comorbidities, the severity of illness and dosage and timing of administration of HCQ (WHO, 2020; New Indian Express, 2020; Mikami et al., 2020). Prior studies have major limitations with timing, dosing, cardiac AE monitoring, and therapeutic windows. To date, there has been no properly designed and powered RCT that evaluates HCQ treatment for COVID-19. Concerning our comments about the Rosenberg paper, a variety of serious limitations in that paper should be corrected on the record. The critical limitation, among many others, is that patients receiving HCQ with or without azithromycin (AZM) were overall sicker on presentation and had multiple other risk factors; Black or Hispanic patients were likely to receive HCQ or AZM (mortality is significantly higher in these groups). Patients receiving HCQ were more likely to be obese, diabetic, have chronic lung disease, and cardiovascular conditions, yet these sicker patients had approximately the same mortality rates compared to patients with a milder course of the disease and fewer risk factors. However, the authors incorrectly conclude that "there are no significant benefits." It is noteworthy that HCQ was associated with a significant survival benefit in a larger cohort of patients from New York City, as reported by Mikami et al. (2020).

In these unprecedented times, the role, cost-benefit, and availability of repurposed agents such as HCQ and newer drugs such as remdesivir should be urgently evaluated in an impartial manner. Remdesivir is a novel drug with a novel approach and has a place in the COVID-19 treatment formulary; however, it is expensive, and there is limited availability outside of the United States (Forbes, 2020; Finley, 2020).

Our paper's overarching theme is that a safe dosage and early utilization of hydroxychloroquine reduced mortality in hospitalized patients. Similar published large cohort studies support our findings from New York City and France (Mikami et al., 2020; Lagier et al., 2020) As stated in our paper, further prospective studies are needed.

Conflict of interest

No conflict of interest to declare.

Ethical approval

Approval was not required.

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