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

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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 (1). 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, co-morbidities: 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 (1), however in this study, HCQ was independently associated with decreased mortality, 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 a 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 duration of symptoms prior to hospitalization. The mSOFA has been validated in other studies (2,3), 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 arrythmias. All centers used the same treatment guideline minimizing treatment bias. The protocol we used was previously published (1). In response to Atkinson, patients assigned to HCQ group had moderate and severe illness at presentation, which would favor worse outcome with HCQ. The exclusion of patients with premorbid risk for cardiac toxicity is similar to clinical trials of many other drugs such as of remdesivir, where individuals with severe liver or kidney disease were excluded (4).

Importantly, in response to Rosenberg, our study differed from other studies including randomized controlled trials (RCTs) in a variety of ways, including number of patients, comorbidities, severity of illness and dosage and timing of administration of HCQ (5-7). 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. In relation to our comments about the Rosenberg paper, there are a variety of serious limitations in that paper that should be corrected on the record. The key limitation among many others are 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 less risk factors. However, the authors 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 (7).

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 (8).

The overarching theme in our paper 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 (7, 10) As stated in our paper, further prospective studies are needed.

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Ethical Approval
Approval was not required.

Conflict of Interest
No conflict of interest to declare.

Declaration of interests
The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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