Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to The Editor

Perceived efficacy of hydroxychloroquine in observational studies: Results of the confounding effect of "goals of care"

Editor: Dr Jim Gray

Dear Editor,

We read with interest the study by Catteau et al. [1] on the association between hydroxychloroquine (HCQ) and in-hospital mortality in 8075 COVID-19 patients from the Belgian National COVID-19 Hospital Surveillance data. A competing risks proportional hazards regression showed mortality was lower in the HCQ group compared with the no-HCQ group (adjusted hazard ratio [aHR] 0.684, 95% confidence interval [CI] 0.617–0.758). The authors concluded that treatment with HCQ was associated with reduced in-hospital mortality.

Nevertheless, we believe that the findings are susceptible to treatment selection bias or "confounding by unmeasured goals of care" [2] and that the authors have made spurious inferences. The authors did not account for "goal of care" information. Such information is of utmost importance during pandemic peaks and when resources are scarce and is usually not readily available in national surveillance data. Decisions to limit life-sustaining therapies have been common during the COVID-19 pandemic and are strongly associated with high mortality risk in ways that are not accounted for by routine measures of illness severity. In fact, in the study by Catteau et al., 90% of non-survivors were aged over 65 years and 80.4% of non-survivors did not receive ventilatory support prior to death. The data summarized in the Table support our contention that physician allocation of patients to the no-HCQ group was biased towards elderly and frail patients, most of whom (80%) did not receive mechanical ventilation and likely died outside the ICU setting. Mortality could not be explained by the clinical features of severe acute respiratory distress syndrome (ARDS) due to COVID-19 as shown in Table 1 and Table 2 of the published study [1].

Allocation of critical care resources has been triaged in many countries during the peaks of the COVID-19 pandemic. The pandemic has put tremendous strain on healthcare systems in many countries, including Belgium, and has led to a shortage of ventilators and ICU resources. During this pandemic, triage has involved adding medical and moral choices to patient preferences for life-sustaining treatment decisions [3]. Many countries have guidelines for triaging patients depending on short-term survival chance versus long-term prognosis criteria that can limit life expectancy [4]. For example, medical urgency, frailty, comorbidities and cognitive impairment (see Table no-HCQ group) were used as criteria for limitation of care in Belgium [4]. Although age was not a criterion, older patients and patients with preexisting serious illness who were more likely to die with an acute illness were more likely to have treatment limitations [2].

We request that the authors account for two important biases that are frequently ignored by investigators: survivor bias and competing risk bias. Survivor bias occurs because patients who live longer are more likely to receive treatment than those who die early. We have shown that this could change associations from benefit to harm [5]. In a sensitivity analysis that considered survivor bias, Catteau et al. reported an aHR 0.816, 95% CI 0.751-0.887 (a 20% increase in the HR). We believe that this should be the primary analysis of the study.

A common approach used by investigators, including Catteau et al., is to examine patient in-hospital mortality data without any follow-up beyond hospital discharge. In this scenario, discharged patients are treated as censored observations when using survival analysis. The fundamental assumption that the death hazard remains the same after censoring is violated here; discharged patients have usually recovered and thus have lower death hazards than patients who remain hospitalized. If no follow-up beyond hospital discharge is available, discharge from hospital and in-hospital mortality are considered "competing events", i.e., events that preclude the occurrence of the event of interest. Investigators should calculate and report aHR for each event to help interpret the associations: HR for death (the event of interest) and HR for discharge (the competing event). Although Catteau et al. have calculated aHR for in-hospital mortality, they have not reported aHR for discharge for any risk factor, including the use of HCQ.

Finally, we emphasize that the "low-dose" regimen of HCQ (400 mg twice on Day 1, followed by 200 mg twice a day from Day 2 to 5) is unlikely to achieve SARS-CoV-2 antiviral activity. We recently reviewed [6] HCQ pharmacological data and concluded that even the lowest in vitro HCQ inhibitory concentration does not seem to achieve a minimum clinical therapeutic concentration of HCQ with dosing of HCQ at >400 mg twice a day. This is because the free lung extracellular trough concentrations from a 400-mg twice-daily dose are well below the in vitro half-maximal effective antiviral concentrations (EC_{50}) (Reviewed in [6]).

We request that investigators are more vigilant when analysing data and interpreting findings from observational studies, particularly when the results contradict those of randomized trials.

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Table 1
Comparison of HCQ and No-HCQ Groups and Survivors and Non-survivors: Focus on Surrogates of "Goal of Care" Confounding

Variable	HCQ Group (n=4542)	No-HCQ (n=3533)	Survivors Group	Non-survivors Group
Age 65-79 years	30.7%	28.8%	28.9%	33.1%
Age >80 years	23.3%	44.6%	24.6%	56.9%
Cognitive disorders	7.8%	17.8%	9.6%	20.8%
Ventilatory support	11.4%	3.3%	5.4%	19.6%

HCQ: Hydroxychloroquine

Declaration of Competing Interests

None

Declarations

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Not required

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Prof. Imad M. Tleyjeh, MD, MSc*
Infectious Diseases Section, Department of Medical Specialties King Fahad Medical City, Riyadh, Saudi Arabia
Division of Infectious Diseases, Mayo Clinic College of Medicine and Science, Rochester, MN, USA
Department of Epidemiology, Mayo Clinic College of Medicine and Science, Rochester, MN, USA
College of Medicine, Al Faisal University, Riyadh, Saudi Arabia

Haytham Tlayjeh, MD
Department of Intensive Care, King Abdulaziz Medical City, Riyadh, Saudi Arabia

*Corresponding Author: Imad M. Tleyjeh, MD, MSc, FACP, FIDSA. Professor of Medicine and Epidemiology, Section of Infectious Diseases, King Fahd Medical City, PO Box 59046, Riyadh 11525, Saudi Arabia. Phone: 00966112889999.
E-mail address: Tleyjeh.imad@mayo.edu (Prof. .M. Tleyjeh)