A recent study [1] has suggested a subjective perspective that nearly 17,000 people in the U.S. and five other countries may have died prematurely during the early stages of the pandemic because of the compassionate use of hydroxychloroquine (HCQ) for treating COVID-19 infection. The study's conclusions are disapproved for relying on flawed data and overlooking substantial evidence supporting the efficacy of HCQ in the early outpatient treatment of the infection.

The study [1] is a retrospective meta-analysis of 44 papers covering COVID-19-infected hospitalized patients from March to July 2020 in the U.S., France, Belgium, Italy, Spain, and Turkey. The study itself acknowledges limitations such as unaccounted influencing factors and uncertain estimates of HCQ exposure. The study's estimates, which are based on guessed rates of HCQ exposure ranging widely, may be overstated or understated by significant factors.

#Our reply

The author provides no arguments to support this assertion.

The impact of other medications like remdesivir and the use of ventilators, both known to increase COVID-19 mortality, is disregarded.

#Our reply

Remdesivir did not increase the risk of mortality in COVID-19 (1). Mechanical ventilation is a management method for severe forms of respiratory distress.

The underlying conditions of those who were administered HCQ are similarly disregarded. The study fails to consider the potential risks associated with patients' pre-existing conditions, such as obesity, diabetes, chronic cardiac diseases, chronic kidney diseases, cancer history, and immunocompromised. The heterogeneous nature of the 44 studies and the confounding factors in nonrandomized, retrospective cross-sectional cohorts raise concerns about the study's reliability in determining the effects of HCQ use for COVID-19 infection.

#Our reply

These ambitious modeling objectives are beyond the scope of our study. It is noteworthy that no interaction factor affecting mortality induced by hydroxychloroquine has been described.

The assertion that HCQ use is causally associated with increased mortality risk is therefore challenged, as every nonrandomized study in the past four years indicates that patients taking HCQ had worse health and chronic conditions, making causal association claims illusory.

The distinction between hospitalized and outpatient COVID-19 is also here emphasized, stating that HCQ's effectiveness lies in outpatient use to prevent hospitalization and mortality.

#Our reply

The consideration of prescriptions outside the hospital setting would, on the contrary, lead to an increase in the number of deaths.

Notably, the study does not acknowledge the early pandemic use of HCQ, often combined with zinc and antibiotics, which has consistently shown positive results in numerous peer-reviewed studies.

#Our reply

All randomized trials have shown at best a neutral effect on mortality. Beyond mortality, trials indicate an increased risk of serious adverse events and mechanical ventilation with HCQ (1).

Specific criticism is also directed at the study's use of an 11% odds ratio derived from a 2021 meta-analysis of randomized trials, wherein 63% of the data came from two trials both sponsored directly or indirectly by the Bill & Melinda Gates Foundation, considered flawed for using potentially fatal HCQ dosages additionally to be likely biased by conflict of interest.

#Our reply

The doses used in the trials are based on PK/PD modeling, allowing for the achievement of therapeutic concentrations (2,3). In France, the pharmacovigilance network has reported 8 deaths and serious adverse events during one month in COVID-19 patients despite national guidance suggesting lower doses (4).

We do not understand how the assistance of a charitable foundation could influence the results of trials of this magnitude.

The study's failure to consider the widespread use of HCQ in various countries, with overall positive results and lower mortality rates, further challenges its conclusions. The work [1] does not consider the prevailing practice of using HCQ early in the pandemic, often in combination with zinc and an antibiotic such as azithromycin (AZM). The work [1] does not even consider all the evidence for late stages of infection.

#Our reply

The combination with azithromycin may possibly be responsible for an increased risk of cardiac adverse effects (4,5). We do not understand the mention of zinc, as it is not a treatment for COVID-19.

Based on all the 568 studies made so far on HCQ for COVID-19, 445 of them peer-reviewed, and 418 of them comparing treatment and control groups, a more objective view [2] suggests

late treatment and high dosages may have been harmful, but early treatment consistently showed positive results, with all the negative evaluations typically ignoring treatment delay [2].

#Our reply

The doses used in the trials are based on PK/PD modeling, allowing for the achievement of therapeutic concentrations (2,3). In France, the pharmacovigilance network has reported 8 deaths and serious adverse events during one month in COVID-19 patients despite national guidance (4). An increase of serious cardiovascular adverse events in the USA was reported (5).

Based on the full body of scientific evidence [2], HCQ provided a statistically significant lower risk for mortality, hospitalization, recovery, cases, and viral clearance. Specifically, HCQ provided a 65% lower risk for early treatment (Confidence Interval CI=54-74%), versus a 20% lower risk for late treatment (CI=16-24%) [2]. In early treatment, HCQ provided a 25% lower risk in 9 Randomized Controlled Trials (RCTs) with CI=18-52%, and 76% lower mortality in 16 early treatment studies, CI=60-86% [2].

#Our reply

Reference [2] is a private website that offers no guarantee or scientific value.

HCQ/CQ was adopted in all or part of 42 countries (57 including non-government medical organizations), with the above overall positive results. Countries that made it very difficult to use antivirals against COVID-19, to favor restrictions and vaccines, such as the U.S., then managed to make 3,430 per million COVID-19 fatalities, while much more pragmatic countries that were much more permissive in the use of antivirals such as United Arab Emirates or Saudi Arabia only had 248 or 264 per million. This is a clear indication that the narrative of a superior approach followed in Western countries to manage COVID-19 infection is flawed, the same as the assessment of the negative impact of using HCQ for COVID-19 infection in the study [1].

#Our reply

This is a personal interpretation of the history of the pandemic. It should be noted that HCQ has never been recognized as a treatment for COVID-19, except for compassionate use during the first wave, in countries where regulatory agencies conducted evidence-based evaluation.

In summary, this critique argues for a more nuanced and objective assessment of HCQ's impact on COVID-19 infection, emphasizing early treatment efficacy and cautioning against generalizations based on selected potentially flawed studies. Delaying treatment and

administering high dosages of HCQ may have been potentially harmful, whereas initiating treatment early with HCQ and other antivirals consistently demonstrated positive outcomes. Negative evaluations with HCQ often overlooked the impact of treatment delays and pre-existing conditions.

#Our reply

We strongly disagree with the author's conclusions regarding the benefit of HCQ in COVID-19.

Our article explicitly mentioned the numerous limitations of the estimation, including in the abstract.

REFERENCE

1. Siemieniuk RA, Bartoszko JJ, Zeraatkar D, Kum E, Qasim A, Martinez JPD, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ* 2020;370:m2980.
2. White NJ, Watson JA, Hoglund RM, Chan XHS, Cheah PY, Tarning J. COVID-19 prevention and treatment: A critical analysis of chloroquine and hydroxychloroquine clinical pharmacology. *PLoS Med* 2020;17:e1003252.
3. RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med* 2020;383:2030–2040.
4. Gérard A, Romani S, Fresse A, Viard D, Parassol N, Granvuillemin A, et al. “Off-label” use of hydroxychloroquine, azithromycin, lopinavir-ritonavir and chloroquine in COVID-19: A survey of cardiac adverse drug reactions by the French Network of Pharmacovigilance Centers. *Therapie* 2020;75:371–379.
5. Zhao Y, Zhang J, Zheng K, Thai S, Simpson RJJ, Kinlaw AC, et al. Serious Cardiovascular Adverse Events Associated with Hydroxychloroquine/Chloroquine Alone or with Azithromycin in Patients with COVID-19: A Pharmacovigilance Analysis of the FDA Adverse Event Reporting System (FAERS). *Drugs - Real World Outcomes* 2022;9:231–241.