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.

International Journal of Infectious Diseases 99 (2020) 38–39

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Letter to the Editor

Clarifying the record on hydroxychloroquine for the treatment of patients hospitalized with COVID-19

To the editors,

The study from Arshad et al. on the use of hydroxychloroquine, with and without azithromycin, for the treatment of inpatients with COVID-19 in one healthcare system (Henry Ford Health System), is a new entrant into the rapidly expanding literature on the treatment of this disease (Arshad et al., 2020; Sattui et al., 2020). The study's findings of a significant beneficial effect of hydroxychloroquine in the reduction of in-hospital mortality are not consistent with several recent studies, and as authors of one of those studies, we wish to share a few observations (Sattui et al., 2020; Geleris et al., 2020; Rosenberg et al., 2020).

In the Discussion section, Arshad et al. distinguish their study from our cohort study of 1438 patients in 25 New York metropolitan region hospitals, which found a generally null association between these medications and mortality (Arshad et al., 2020; Rosenberg et al., 2020). In doing so, the authors make multiple statements that are not factually aligned with our published research. Arshad et al. state that the Rosenberg et al. " . . . study included patients who were initiated on hydroxychloroquine therapy at any time during their hospitalization. In contrast, in our patient population, 82% received hydroxychloroquine within the first 24 hours of admission, and 91% within 48 hours of admission." (Arshad et al., 2020). Although we included those who received hydroxychloroquine or azithromycin at any time during hospitalization, we reported detailed information on the length of time from admission to initiation of either therapy (as well as on dosage patterns). In fact, patients in our study had been generally initiated rapidly: "Hydroxychloroquine was initiated at a median of 1 day (Q1-Q3, 1-2) following admission and azithromycin was given at a median of 0 days (Q1-Q3, 0-1)." (Rosenberg et al., 2020). This distribution is quite similar to that of the Henry Ford study.

The authors next state the following about our work: "Because treatment regimens likely varied substantially (including delayed initiation) across the 25 hospitals that contributed patients to the study, it is not surprising that the case-fatality rate among the New York patients was significantly higher than in our study." This statement neglects the extensive statistical adjustment for between-facility variation in our publication, the generalizability benefit of including 25 hospitals into the cohort with differing therapeutic protocols and approaches, and it misrepresents the fatality rate in our study. We reported 20.3% (95% CI: [18.2–22.4%]) fatality from 292 deaths in 1,438 patients, whereas Arshad et al. report 18.1% from 460 deaths in 2541 patients in a later era of the COVID-19 epidemic. We fail to find a difference between these studies' fatality rates both practically and statistically (χ^2 df = 1 test $p = 0.09$).

These erroneous representations of previous work should be clarified as they have appeared to have led to confusion in subsequent characterizations of the Arshad et al. paper relative to our study (Henry Ford Health System, 2020; Wells and Erb, 2020).

Also, in the accompanying editorial, Lee et al. reviewed important potential limitations to the Arshad et al. study (Lee et al., 2020). We underscore the concerns raised that bias may have been introduced into the study's design by reserving the combination of hydroxychloroquine and azithromycin for patients with "minimal cardiac risk factors." Additionally, Lee et al. discuss the possibility that there may have been palliative intent in selecting neither hydroxychloroquine nor azithromycin for patients who were more ill (given counterintuitive observed ICU admission and fatality rates by treatment group). Finally, Lee et al. note that 78.9% and 74.3% of the patients in the hydroxychloroquine and combined hydroxychloroquine and azithromycin groups (respectively) received steroid therapy, while 35.7% of patients in the 'neither' group received steroid therapy. Given promising results from a recent multi-site randomized study in the United Kingdom supporting a mortality benefit of dexamethasone, this confounding variable is of substantial concern (Horby et al., 2020).

These potential confounding bias-concerns regarding Arshad et al. highlight the vital role of randomized clinical trials as the gold standard study design for evaluating the benefit of COVID-19 therapeutics. In the month before *IJID's* June 29 acceptance of Arshad et al., two large-scale randomized trials in the United Kingdom (RECOVERY) and United States (ORCHID) of hydroxychloroquine for inpatient treatment of COVID-19 were stopped early due to lack of efficacy (Trial, 2020; NIH, 2020). On July 4, the WHO similarly halted the hydroxychloroquine arm of their Solidarity Trial (WHO, 2020). Evidence from RECOVERY was a key factor that weighed in the US Food and Drug Administration's (FDA) June 15 decision to revoke hydroxychloroquine's Emergency Use Authorization (EUA) for COVID-19 treatment (FDA, 2020).

We appreciate the opportunity to clarify the record regarding our study as described by Arshad et al. and to join with Lee et al. in expressing methodological concerns about the Arshad et al. study. Such scientific dialogue is critical to the advancement of the field and thereby appreciated.

Conflict of interest

None.

http://dx.doi.org/10.1016/j.ijid.2020.07.055

Funding source

No related funding.

Ethical approval

No ethical approval was obtained, as no new human subjects research was conducted.

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Received 13 July 2020