Front. Med.
https://doi.org/10.1007/s11684-025-1123-9

Low dose of hydroxychloroquine is associated with reduced COVID-19 mortality: a multicenter study in China

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Dear Editor,

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has widely spread worldwide, and we have been fighting against coronavirus disease 2019 (COVID-19) for more than 4 years [1]. According to the statistics of the World Health Organization (WHO), more than 775 million individuals have incurred COVID-19, and 7 million deaths have been recorded. The COVID-19 outbreak has become a devastating global health crisis, and the challenges faced by humanity due to this disease are continuing [2]. In the past 4 years, an old antimalarial drug, hydroxychloroquine (HCQ), has been evaluated by doctors and scientists [3]. Its effects on the immune system have been fully confirmed, including inhibition of Toll-like receptor signals and lymphocyte receptors; interference with lysosomal acidification, antigen presentation, and DNA binding and stabilization; and reduction of pro-inflammatory cytokines produced by macrophages (especially IL-1, IL-6, and TNF-α) [4]. *In vitro* experiment of HCQ showed its efficacy in inhibiting novel coronaviruses and its greater effectiveness than chloroquine [5]. Our previous clinical results also supported that HCQ has good therapeutic effects on patients with COVID-19 [6]. An observational study revealed that the use of HCQ was associated with a reduced hospitalization rate among patients with COVID-19 [7]. Nevertheless, some studies reported neutral or negative findings on the clinical results and meta-analysis of patients with COVID-19 treated with HCQ [8], leading to doubts and restrictions on the clinical use of HCQ on patients with COVID-19 to a certain extent.

We conducted a multicenter retrospective study of 53 030 patients with COVID-19 (discharged or deceased) in 138 hospitals in Hubei Province to clarify the effects of different HCQ doses on the mortality of patients with COVID-19 (Trial registration: NCT05615792). Under China and WHO interim guidance, all the patients diagnosed with COVID-19 between Dec 29, 2019 (i.e., when the first patients were admitted) and Aug 31, 2021 were screened, and those who had died or were discharged were included in this study. The patients were divided into HCQ group and non-HCQ group according to whether or not they were administered with HCQ. A 1:1 propensity score matching (PSM) analysis was used to balance the confounding factors between HCQ group and non-HCQ group. The HCQ group consisted of patients with COVID-19 who continuously received HCQ for more than 3 days. According to the dosage, the HCQ group was subdivided into high-dose (⩾ 400 mg/d) and low-dose (< 400 mg/d) groups.

This study included 68 128 patients with COVID-19 from 138 hospitals in Hubei Province diagnosed before August 31, 2021. Among these patients, 15 098 (22.2%) were excluded because of missing data. Finally, 53 030 inpatients were included in the analysis, of whom 52 189 were classified into the HCQ group and non-HCQ groups (Fig. 1). To reduce the effects of confounding factors, we conducted a rigorous and high-quality 1:1 PSM. The baseline characteristics and treatments of the groups after PSM are shown in Table S1. Among the entire cohort, 3710 patients died during hospitalization (7.0%), of whom 46 (5.5%) were in the HCQ group and 3664 were in the non-HCQ group (7.0%) (P = 0.001). The median hospital stay was 22 (IQR, 14–32) and 13 (IQR, 7–20) days for the HCQ and non-HCQ groups, respectively (P < 0.001). Kaplan–Meier survival curve and proportional Cox regression analyses (none of which violated the proportional hazard hypothesis) showed that the all-cause mortality during hospitalization was significantly lower in

Received August 5, 2024; accepted December 16, 2024

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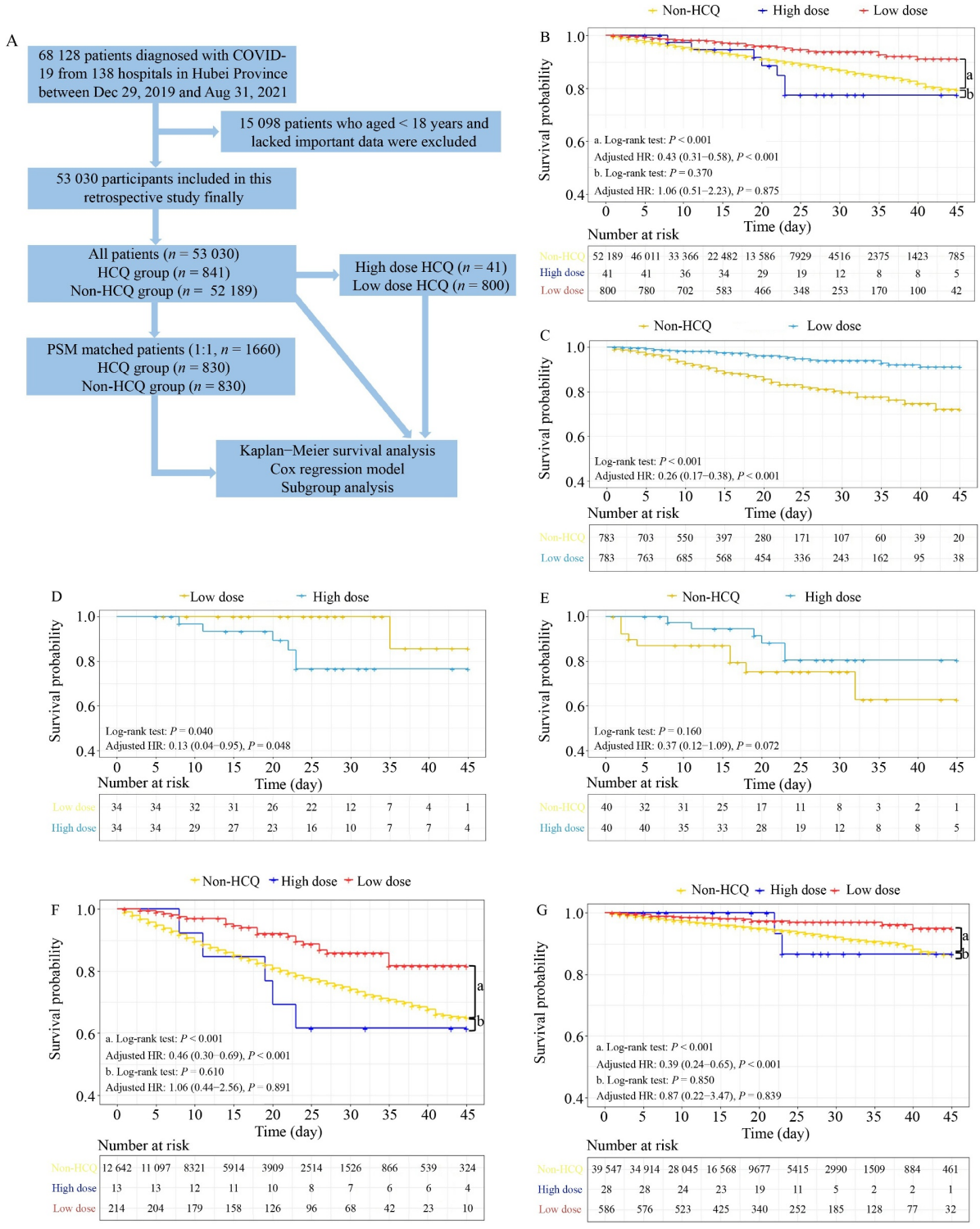

Fig. 1 Effect of different doses of HCQ on mortality of patients with COVID-19. (A) Flowchart of study design. (B) Kaplan–Meier survival curve of in-hospital mortality for patients with COVID-19 in the low- and high-dose HCQ groups and non-HCQ group. (C) Kaplan–Meier survival curve of in-hospital mortality for patients with COVID-19 in the low dose group and non-HCQ group after PSM. (D) Kaplan–Meier survival curve of in-hospital mortality for patients with COVID-19 in the low- and high-dose groups after PSM. (E) Kaplan–Meier survival curve of in-hospital mortality for patients with COVID-19 in the non-HCQ group and high-dose group after PSM. (F) Kaplan–Meier survival curve of in-hospital mortality for patients with mild COVID-19 in the low- and high-dose HCQ groups and non-HCQ group. (G) Kaplan–Meier survival curve of in-hospital mortality for critically ill patients with COVID-19 in the low- and high-dose HCQ groups and non-HCQ group.

the HCQ group than in the non-HCQ group (log-rank $P <$ 0.001; adjusted HR, 0.47; 95% CI, 0.35–0.63; $P < 0.001$) (Fig. S1A). PSM analysis results also supported that HCQ use was associated with a low all-cause mortality in patients with COVID-19 during hospitalization (log-rank $P < 0.001$; adjusted HR, 0.34; 95% CI, 0.24–0.49; $P <$ 0.001) (Fig. S1B).

The HCQ group was subdivided into the low- and high-dose groups to explore the effect of different HCQ doses on the clinical outcome of patients with COVID-19. The baseline characteristics and treatments of the low- and high-dose HCQ groups are shown in Table S2. Survival analysis of the primary and secondary clinical endpoints was performed in the high-dose, low-dose, and non-HCQ groups. Kaplan–Meier survival curve and multivariate Cox model analyses showed that the all-cause mortality during hospitalization was significantly lower in the low-dose group than in the non-HCQ group (log-rank $P <$ 0.001; adjusted HR, 0.43; 95% CI, 0.31–0.58; $P < 0.001$). Meanwhile, no significant difference in all-cause mortality was found between the high-dose group and non-HCQ group (log-rank $P = 0.370$; adjusted HR, 1.06; 95% CI, 0.51–2.23; $P = 0.875$) (Fig. 1B). In addition, we obtained three cohorts using 1:1 PSM to further compare the differences in all-cause mortality between the two groups. The results indicated that the low-dose group was still associated with a lower all-cause mortality compared with the non-HCQ group (log-rank $P < 0.001$; adjusted HR, 0.26; 95% CI, 0.17–0.38; $P < 0.001$) and high-dose group (log-rank $P = 0.040$; adjusted HR, 0.26; 95% CI, 0.17–0.38; $P = 0.052$) (Fig. 1C and 1D). No significant difference in mortality was observed between the high-dose group and non-HCQ group (log-rank $P = 0.160$; adjusted HR, 0.37; 95% CI, 0.12–1.09; $P = 0.072$) (Fig. 1E).

According to disease severity, the patients with COVID-19 were divided into mild and critically ill subgroups for survival analysis. Kaplan–Meier survival curve and multivariate Cox model analyses showed that the use of low-dose HCQ in the mild subgroup (log-rank $P < 0.001$; adjusted HR, 0.46; 95% CI, 0.30–0.69; $P <$ 0.001) and critically ill subgroup (log-rank $P < 0.001$; adjusted HR, 0.39; 95% CI, 0.24–0.65; $P < 0.001$) was associated with lower mortality compared with the non-HCQ group (Fig. 1F and 1G). No significant difference in all-cause mortality was found between the high-dose group and non-HCQ group among the mild and critically ill patients (Fig. 1F and 1G). After performing PSM, we also found that the mortality in the low-dose HCQ group was significantly lower than that in the non-HCQ group among the mild and critically ill patients (Fig. S2A and S2B). Low-dose HCQ was associated with lower all-cause mortality than no HCQ and high-dose HCQ in patients with impaired heart function (NT-proBNP > 285 ng/L) and liver function (ALT > 40 ng/L) (Fig. S3A and S3B). We chose acute respiratory distress syndrome, invasive mechanical ventilation, acute heart injury, and acute kidney injury as secondary outcomes. Multivariate Cox regression results showed that low-dose HCQ was associated with low invasive mechanical ventilation (adjusted HR, 0.73; 95% CI, 0.54–0.99; $P = 0.043$), acute heart injury (adjusted HR, 0.61; 95% CI, 0.40–0.95; $P =$ 0.028), and acute renal injury (adjusted HR, 0.70; 95% CI, 0.54–0.91; $P = 0.008$) (Table S3).

HCQ is a commonly used anti-malarial drug with anti-inflammatory and antiviral effects. Among these effects, HCQ exhibits an anti-inflammatory function mainly by inhibiting the release of immune cells and related pro-inflammatory cytokines, and its antiviral effect is mainly achieved by suppressing viral endocytosis [4]. Hence, HCQ has become a potential therapeutic drug of choice during the COVID-19 outbreak. However, its effect on the treatment of patients with COVID-19 is still controversial. Some studies have shown that HCQ was not beneficial in reducing the mortality of patients with COVID-19 [8,9]; however, they did not consider the HCQ dosage or used excessive doses (800 mg/d). Nevertheless, we observed that low-dose HCQ (< 400 mg/d) was significantly associated with a low risk of all-cause mortality in hospitalized patients with COVID-19 in the Hubei Province.

Research has indicated the potential benefits of HCQ for patients with COVID-19. A multicenter observational study showed that HCQ use was associated with reduced hospitalization rates [7]. In addition, a correlation was found between the treatment effect of HCQ and the number of days of onset of treatment [10]. A study from France showed that HCQ treatment was significantly related to a reduction or disappearance of SARS-CoV-2 load, and azithromycin enhanced this effect [11]. In addition, HCQ use was associated with reduced hospitalization in intensive care units, early discharge, and decreased C-reactive protein [12]. A study in Italy found that HCQ had a particularly beneficial effect on low-risk patients with COVID-19, helping clarify the controversy surrounding HCQ use in COVID-19 treatment [13]. Moreover, country-based COVID-19 mortality is relatively low in countries where HCQ is widely used early on [14]. The observed association between low-dose HCQ and reduced mortality, contrasted with the lack of such association at high doses, raises important considerations. One possible explanation for this finding could be the differing safety profiles and therapeutic windows associated with varying HCQ dosages. At low doses, HCQ may confer beneficial anti-inflammatory or antiviral effects that contribute to improved patient outcomes without significant adverse effects. By contrast, high doses could potentially lead to

toxicities that negate these benefits, such as cardiac side effects or other systemic issues [15]. Potential variations in patient populations or comorbidities that may influence how different doses impact mortality must also be considered. Further research is needed to delineate these mechanisms and to identify the optimal dosing strategy that maximizes efficacy while minimizing risks.

This study had several limitations. First, this work was a retrospective study, and all the data were obtained from a clinical database. All the laboratory data had not been collected, and some imaging results were unavailable. In addition, differences were noted in the quality of data among the different hospitals and in the treatments. Furthermore, we only focused on HCQ dose and did not compare the effects of HCQ combined with other drugs (such as azithromycin) on the mortality of patients with COVID-19. Finally, all the patients with COVID-19 were hospitalized in the Hubei Province. Our analysis did not compare the data from other provinces or foreign countries with those from the Hubei Province.

In conclusion, our study compared the effects of different HCQ doses on clinical outcomes. Results showed that low-dose HCQ was associated with low mortality, invasive mechanical ventilation, acute heart injury, and acute renal injury. This work provided clinical evidence for the therapeutic effect of different HCQ doses on patients with COVID-19. We recommend early use of low-dose HCQ in patients with COVID-19.

Acknowledgements

The authors would like to thank all patients, their families, and all investigators involved in this study. The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article. This work was supported in part by the projects of National Natural Science Foundation of China (Nos. 82100526, 82241034, and 82330010) and National Key R&D Program of China (No. 2024YFC3044500).

Compliance with ethics guidelines

Conflicts of interest Wu He, Ke Xu, Yongcui Yan, Gen Li, Bo Yu, Junfang Wu, Kaineng Zhong, Da Zhou, and Dao Wen Wang declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Dao Wen Wang is a member of the Editorial Board of Frontiers of Medicine, who was excluded from the peer-review process and all editorial decisions related to the acceptance and publication of this article. Peer-review was handled independently by the other editors to minimise bias.

The study was approved by the Research Ethics Committee of Tongji Medical College (No. TJ-IRB20210138) and the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Due to the retrospective nature of this study and the anonymity of its participants, the ethics committee waived the requirement for written informed consent.

Electronic Supplementary Material Supplementary material is available in the online version of this article at https://doi.org/10.1007/s11684-025-1123-9 and is accessible for authorized users.

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