



## Hydroxychloroquine's Probable Protective Effect in Liver injury among the COVID-19 Patients

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### INTRODUCTION

Coronavirus disease 2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global emergency. The majority of the respective studies are focused on respiratory complications. However, COVID-19 might affect other organs namely the liver and kidneys. Liver damage caused by other species of the coronavirus family has been reported in the literature.<sup>1,2</sup> Evidence of liver damage and elevated liver enzymes are also present in the studies of numerous COVID-19 patients. While clinically significant liver injury has not been reported in COVID-19 patients without underlying liver diseases, various studies have shown higher aminotransferase levels in many COVID-19 patients who had impaired baseline liver function tests (LFTs) and no known history or present symptoms of liver diseases, as well as critically ill patients.<sup>3-7</sup>

Hypoxic hepatitis (HH) is a common phenomenon in ICU-admitted patients. Anoxic damage of centrilobular liver tissue during HH causes a rapid and short-lasting influx of serum aminotransferases. Besides, pre-existing cardiopulmonary failure and toxic-septic shock are the primary conditions responsible for most of the cases. Seemingly, this is one of the possible causes of elevated liver enzymes in severe ICU-admitted COVID-19 patients.

Having contradictory roles, autophagy has an irrefutable role in liver diseases. On the one hand, acting as an easily-enabled cytoprotective system, autophagy is activated by numerous causes and plays an important role in various liver diseases, but on the other hand, it can be protective during hepatic ischemia/reperfusion injury.<sup>8</sup>

Chloroquine (CQ) is a classic antimalarial drug that has been repurposed as an immunomodulator in Rheumatology. Recently, CQ is introduced and suggested as a possible beneficial drug for the management of COVID-19 patients. Chloroquine is well-known as an inhibitor of autophagy and a drug with anti-inflammatory properties. In a study published in June 2013, Fang et al demonstrated that after one hour of warm ischemia, chloroquine reduces liver



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injury within the first 6 hours after administration, but aggravates it 1 or 2 days after liver reperfusion.<sup>9</sup> Acting like a double-edged sword, while chloroquine could protect the liver during ischemia/reperfusion injury through the inhibition of inflammatory responses in the early hours after administration, it could later aggravate liver damage via inhibition of autophagy and the resultant induction of apoptosis.<sup>10</sup> These different effects of chloroquine on the liver injury at different times signify the value of repeated LFTs after the diagnosis and treatment initiation. Liver function tests in the recent literature could be reported from previously referred and potentially treated with hydroxychloroquine patients who have received the drug just hours before sampling (especially in the outpatient management of COVID-19). Thus, the protective effect of chloroquine on ischemic hepatitis may have masked the hepatic liver injury of coronavirus infection. To avoid misleading paraclinical data and identify the possible liver damage in COVID-19 pneumonia, serial liver function tests at close intervals are recommended.

Emphasizing on chloroquine's inhibitory effects on HMGB1-mediated inflammatory responses and its facilitatory effects on pro-apoptotic pathways, another study has shown chloroquine's possible clinical utility for acute liver injury. As liver injury carries on, chloroquine could regulate the resultant apoptotic and inflammatory responses.<sup>11</sup>

We suspect that the probable protective effects of prophylactic hydroxychloroquine for the liver might be helpful to reduce the incidence of potential liver failure in COVID-19 patients with hepatic comorbidities.

#### ETHICAL APPROVAL

There is nothing to be declared.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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