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Letter: liver involvement and mortality in COVID-19—the role of anti-viral therapy should be considered

To the Editor,

We read with interest the article by Ponziani et al[1]; the conclusion of the authors was different from other previous studies,[2,3] but baseline characteristics of these populations are slightly different. The main aspect is the assessment of abnormal liver function tests (LFTs) at hospital admission or during hospitalisation. In the first case, as observed by Piano et al,[3] alanine aminotransferase (ALT) elevation was found in 58% of patients on admission, but 326 of 565 patients took medications with potential risk of liver injury such as acetaminophen (15%), antibiotics (24%), statins (15%) or NSAIDs. In the second hypothesis, the LFT alteration maybe due to the severity of SARS-CoV-2 infection, with the presence of systemic inflammatory response syndrome or acute respiratory distress syndrome (ARDS). Obviously, the different severity presentation of enrolled patients isdetermined by the incidence of liver injury. In the study of Ponziani et al, only 146 patients with ARDS (32.6%) were included; in the study of Piano et al, there were 375 patients (66%) with sequential organ failure assessment score (SOFA) ≥2. Therefore, the impact of abnormal LFTs on ICU admission and mortality may be attributable to the clinical severity. Finally, drug-induced liver injury (DILI) should be considered in patients with normal baseline LFTs that increase during hospitalisation in the absence of other major cause of liver involvement (*e.g.*, ARDS and sepsis).[4] Although the ALT increase was detected in 20.4% of patients during their hospital stay, the risk of DILI was not assessed in this analysis.[1]

We report our experience of treating 329 patients affected by COVID-19 pneumonia without ARDS and with normal LFTs on admission. Most (270, 82%) were treated from March to June 2020 with the available drug combinations according to different comorbidities and clinical presentation as follows: 139 (51.5%) received hydroxychloroquine (HCQ) alone (200 mg *b.d.* for 7 days), 41 (15.2%) the combination of HCQ and lopinavir/ritonavir (LPV\r 200 mg\50 mg *b.d.* for 7 days) or HCQ plus darunavir\cobicistat (DRV\c 800 mg\150 mg *q.d.* for 7 days). After a median of 6-9 days, abnormal LFTs were detected in 11 patients taking HCQ alone (7.9%), but all had ALT levels <5x UNL. In four patients on HCQ + LPV\r (9.7%) and in 22 (24.4%) treated with HCQ + DRV\c, two had a hepatitis flare with ALT level >10x UNL, with resolution after a few days of treatment interruption; in these patients, bilirubin and GGT elevations were also observed. Interestingly, the median ALT elevation during the treatment period was significantly different among the different drug combinations, as depicted in Figure 1. Median ALT

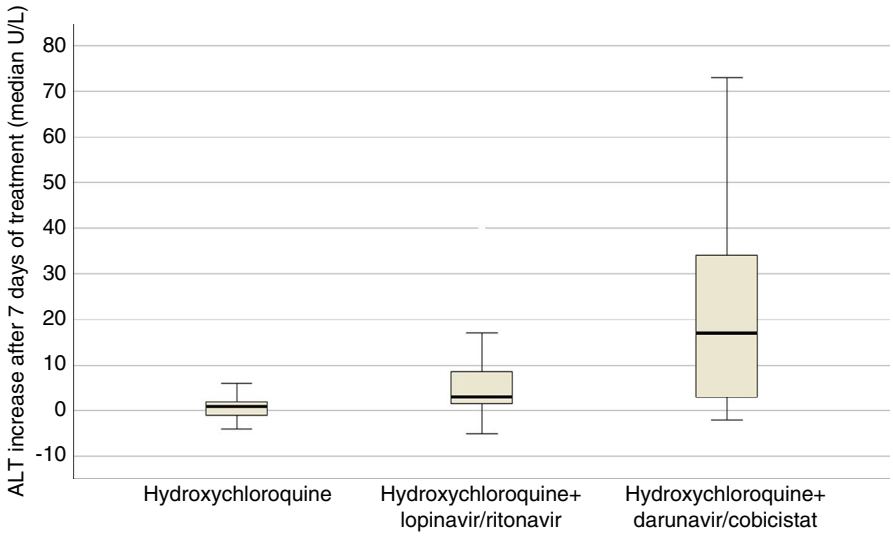

FIGURE 1 Median ALT value elevations in COVID-19 patients according to different anti-viral treatment

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increase on HCQ alone was 2.2 IU (IQR: 0-4.6); on HCQ + LPV\r, it was 3.6 IU (IQR: 1.9-7.8); and on HCQ + DRV\c, it was 18.5 IU (IQR: 2.5-35) ($P < 0.001$ for DRV\c vs others).

In conclusion, we suggest that the severity baseline score of patients and DILI should be considered as important causes of hepatotoxicity in patients with COVID-19.

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LINKED CONTENT

This article is linked to Ponziani et al paper. To view this article, visit https://doi.org/10.1111/apt.15996

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REFERENCES

1. Ponziani FR, Del Zompo F, Nesci A, et al. Liver involvement is not associated with mortality: results from a large cohort of SARS-CoV-2-positive patients. *Aliment Pharmacol Ther.* 2020;52:1060-1068.
2. Lei F, Liu Y-M, Zhou F, et al. Longitudinal association between markers of liver injury and mortality in COVID-19 in China. *Hepatology.* 2020;72:389-398.
3. Piano S, Dalbeni A, Vettore E, et al. Abnormal liver function tests predict transfer to intensive care unit and death in COVID-19. *Liver Int.* 2020;40:2394-2406.
4. Sun J, Aghemo A, Forner A, Valenti L. COVID-19 and liver disease. *Liver Int.* 2020;40(6):1278-1281.