DOI: 10.1111/apt.16014

INVITED EDITORIAL

AP&T Alimentary Pharmacology & Therapeutics WILEY

Editorial: intended victim or innocent bystander? The liver in COVID-19

Two recent, single-centre retrospective studies from China and Italy assessed the relationships between liver enzyme abnormalities and mortality in COVID-19 patients.[1,2] Although the authors used identical thresholds to define liver enzyme abnormalities and liver injury, they arrived at slightly different conclusions. Huang et al reported that liver injury (>3× ULN for ALT) was associated with significantly increased adjusted hazards of mechanical ventilation and death.[1] They opined that this may reflect a SARS-CoV-2 viral hepatitis. Ponziani et al also showed that admission liver enzymes abnormalities were associated with significantly increased odds of ICU admission, but did not replicate the findings that peak or baseline transaminases were significantly associated with mortality.[2] They observed that enzyme derangements were mild, transient and temporally associated with IL-6 levels, potentially suggesting an inflammatory mechanism. Why were the findings so different?

Although there were key differences between the studies (see Table 1), there was also convergence. 95 ± 3% of patients in both series did not experience liver injury. Both observed that enzyme levels (particularly ALT) increased with disease severity, whether assessed by ICU admission or severity grading. Enzyme levels in both hospitalised cohorts tended to increase over the first 2-3 weeks of admission before slowly normalising. Both studies reconfirmed that COVID-19 is more likely to be severe and fatal in older and male patients and showed associations between white cell abnormalities (relative lymphopenia and relative neutrophilia) and adverse outcomes. This leaves the divergence in findings regarding the relation between (peak) liver enzyme levels and mortality. However, the Italian study did find that baseline liver enzyme derangement was significantly associated with ICU admission, which itself was significantly associated with mortality. The results of these studies are, therefore, broadly in agreement—in

TABLE 1 Comparison of Huang et al's[1] and Ponzani et al's[2] studies published in this edition of the journal. Key differences in determinants of immune function and poor COVID-19 outcome such as age and gender are notable which in addition to other unmeasured factors may have contributed to some differences in results between the studies

	Huang et al[1]	Ponziani et al[2]	*P* value[a]
Setting	Wuhan, China	Rome, Italy	n/a
Number hospitalised: n	675	448	n/a
Age of all hospitalised: (Median (IQR))	Not expressed, but ~10 years less than in (2) at each quartile	68 (55-78)	n/a
Males: n (%)	313 (46%)	286 (64%)	<0.0001
Known CLDx	27 (4%)	6 (1.3%)	0.0106
Antiviral use	Not stated, likely high/routine	Routine, protocolised	n/a
Number hospitalised with no admission liver abnormalities: n (%)	422 (63%)	294 (66%)	ns
Number hospitalised with admission liver injury: n (%)	25 (3.7%)	10 (2.2%)	ns
Severe status or ICU admission: n (%)	53 (8%)	77 (17%)	<0.0001
30-d mortality, estimated from article figures (%)	~15%	Unknown but >15%	n/a

[a]Between study comparisons were made with Fisher's exact test, using Graph Pad Prism v 8.4.2.

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COVID-19, liver derangements are common, usually mild, are associated with severity, and gradually resolve in survivors.

What do these results mean for understanding COVID-19-related enzyme abnormalities? Acute liver failure has not been appreciably reported in COVID-19 despite ~12 000 000 known global cases in 6 months (expected to equate to ~1.2 000 000 cases SARS-CoV-2 associated liver enzyme abnormalities on the basis of Ponziani's non-hospitalised patients).[3] Post-mortem studies remain equivocal,[4] and suspicions of SARS-CoV-2 hepatitis are unlikely to abate.[5] However, potentially contributory aetiologies for COVID-19-related enzyme abnormalities abound, particularly in severe SARS-CoV-2-related illness. These include systemic inflammatory response with risk of hepatic ischaemia and hypoxia, widespread microthrombi formation and drug-induced liver injury.[6] Liver enzyme abnormalities are commonly associated with adverse outcomes in non-viral systemic diseases,[7] and COVID-19 prediction tools incorporate bilirubin rather than transaminases.[8] It is perhaps possible that the predominant aetiology may vary over disease course, with an early viral and later more inflammatory phase of SARS-Cov-2 illness[6]. Notably the most efficacious treatment demonstrated for COVID-19 is an immunosuppressant rather than an anti-viral, the effect size of which is greatest in patients where liver dysfunction is most common.[9,10] Regardless of one's views regarding the existence of SARS-CoV-2 viral hepatitis, clinical evidence still suggests that abnormal liver enzymes in acute COVID-19 remain a sideshow.

ACKNOWLEDGEMENT

Declaration of personal interests: None.

LINKED CONTENT

This article is linked to Huang et al papers. To view these articles, visit https://doi.org/10.1111/apt.15962 and https://doi.org/10.1111/apt.16046

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REFERENCES

1. Huang H, Chen S, Li H, et al. The association between markers of liver injury and clinical outcomes in patients with COVID-19 in Wuhan. *Aliment Pharmacol Ther*. 2020;52:1051–1059.
2. 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. https://doi.org/10.1111/apt.15996
3. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard: World Health Organization; 2020 [updated 2020/7/8]. https://covid19.who.int/
4. Bangash MN, Patel JM, Parekh D, et al. SARS-CoV-2: is the liver merely a bystander to severe disease? *J Hepatol*. 2020.
5. Yang L, Han Y, Nilsson-Payant BE, et al. A human pluripotent stem cell-based platform to study SARS-CoV-2 tropism and model virus infection in human cells and organoids. *Cell Stem Cell*. 2020;27:125–36 e7.
6. Morgan K, Samuel K, Vandeputte M, Hates PC, Plevris JN. SARS-CoV-2 infection and the liver. *Pathogens*. 2020;9:430.
7. Seymour CW, Kennedy JN, Wang S, et al. Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. *JAMA*. 2019;321:2003–17.
8. Liang W, Liang H, Ou L, et al. Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. *JAMA Intern Med*. 2020.
9. Mahase E. Covid-19: Demand for dexamethasone surges as RECOVERY trial publishes preprint. *BMJ*. 2020;369:m2512.
10. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - preliminary report. *N Engl J Med*. 2020.