Commentary:

COVID-19 and liver disease

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Since December 2019, patients with unexplained pneumonia have been found in Wuhan, Hubei Province, China, which was caused by a novel coronavirus that had not been previously identified (1). Tentatively defined as 2019 novel coronavirus (2019-nCoV), the pathogen has now been named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) (2), while the disease termed Coronavirus Disease 2019 (COVID-19). On March 12th, 2020, the World Health Organization (WHO) declared that the COVID-19 constitutes a pandemic. As of April 5th, 2020, the world has reported 1,218,090 confirmed cases of COVID-19 with 65,836 deaths (case fatality rate 5.4%), finding health care systems unprepared to tackle this threat. For that reason, governments, doctors, health workers, scientists, and all citizens must cooperate worldwide to slow-down COVID-19 spread, contain the damage, and find effective cures and preventive measures.
Here we will provide a short and schematic overview of the implications for clinical hepatologists and researchers in the field based on the first available data.

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Clinical features and liver injury in patients with COVID-19

COVID-19 is typically characterized by the symptoms of viral pneumonia such as fever, fatigue, dry cough, anosmia, headache, which may evolve to respiratory failure (3, 4). Due to the ubiquitous distribution of the main viral entry receptor, namely angiotensin converting enzyme 2 (ACE2), SARS-CoV-2 causes a systemic disease, with possible involvement of the heart, the liver, the pancreas and the kidneys, as well as determines alterations in circulating lymphocytes and the immune system (4-7).

COVID-19 associated liver injury is defined as any liver damage occurring during disease progression and treatment of COVID-19 in patients with or without pre-existing liver diseases. Overall, the incidence of elevated serum liver biochemistries in hospitalized patients with COVID-19, primarily elevated AST and ALT, and slightly elevated bilirubin, ranges from 14% to 53% (4, 8-14). Increased liver enzymes are observed more commonly in males and in more severe than in milder cases. Low albumin is a maker of severe infection and poor prognosis (15). Up to now, there is no report of acute or acute on chronic liver failure in COVID-19 patients (4, 8-13).

The largest cohort study enrolling 1,099 COVID-19 cases from China showed that 21 (2.1%) had pre-existing hepatitis B. The overall ALT elevation occurred in 21.3% (158/741), AST elevation 22.2% (168/757). Severe patients had a higher probability of ALT elevation, compared with non-severe patients (28.1% vs 19.8%), as well as of AST elevation (39.4% vs 18.2%). Overall, 10.5% (76/722) patients presented with abnormal bilirubin (14).

Mechanisms of liver injury

The liver biopsy specimens of patients deceased due to severe COVID-19 showed moderate microvascular steatosis and mild lobular and portal activity, indicating the injury could have been caused by either SARS-CoV-2 infection or drug-induced liver injury (3). Several possible mechanisms are indicated as below.

a) Immune mediated damage due to the severe inflammatory response following COVID-19 infection (6): the inflammation biomarkers including C reactive protein (CRP), serum ferritin, LDH, D-dimer, IL-6, IL-2, were significant elevated in severe patients with COVID-19 (16).

b) Direct cytotoxicity due to active viral replication in hepatic cells: SARS-CoV-2 binds to target cells through ACE2. Because ACE2 is expressed abundantly in the liver and in particular on biliary epithelial cells, the liver is a potential target for direct infection (17), which was however not yet demonstrated.

c) Anoxia: the hallmark of COVID-19 is respiratory failure. Hypoxic hepatitis due to anoxia is therefore frequent in severe cases.

d) Drug induced liver injury (DILI): initial clinical guidelines recommended antiviral agents for COVID-19, with some of them, including lopinavir/ritonavir, remdesivir, chloroquine, tocilizumab, uminefovir, Chinese traditional medicine, being potentially hepatotoxic in some patients (and a few have subsequently already been proven to be ineffective).

e) Reactivation of pre-existing liver disease: patients with pre-existing chronic liver disease, may be more susceptible to liver damage from SARS-CoV-2 (18). Biological drugs like tocilizumab and baricitinib might also cause HBV reactivation and thus lead to liver function deterioration. On the other hand, it is still unknown whether SARS-CoV-2 infection exacerbates cholestasis in those with underlying cholestatic liver diseases.

Clinical implications for the management of liver injury during COVID-19

a) Regular monitoring of liver biochemistries should be performed in all COVID-19 patients.

b) Serologic testing for hepatitis B and C and investigation of other causes of liver disease, which should take into consideration the local epidemiology, is warranted when assessing patients with COVID-19 and elevated liver biochemistries.
c) Up to now, data on the safety of drugs currently used for the treatment of SARS-CoV-2 infection in COVID-19 patients with liver injury are missing. All approaches are empirical.
d) The presence of abnormal liver biochemistries does not seem to represent a contraindication to using investigational or off-label therapeutics for COVID-19, although strict monitoring is advisable.
e) The outcome of patients with liver injury is satisfactory, alterations of liver enzymes seem usually transient and severe liver injury is rare. No death was documented to be directly related to hepatic decompensation in patients without pre-existing liver disease so far.

Prevention measures to consider in liver clinics

During the COVID-19 pandemia, the risk of delivering suboptimal care to patients with other diseases is significant. This is especially true for liver diseases for several reasons:

a) Liver specialists, who are generally characterized by broad clinical knowledge, are likely to be heavily involved in the in-hospital management of COVID-19 patients;
b) Most liver diseases are managed in outpatient clinics that will be dramatically reduced in capacity;
c) The perception that chronic liver diseases are associated with higher mortality after COVID-19 infection might lead to physicians and patients postponing visits and procedures. The last point is not supported by the currently available literature (19) and by previous reports on other coronaviruses infections, and should therefore not be considered an absolute barrier to care during the COVID-19 pandemia.

Thus, when designing the activity of a liver clinic during the pandemia, efforts should be made to deliver high level individual care whilst also containing viral spread. In keeping with detailed recommendations of major scientific societies (20, 21) and clinical experience, we propose that:

i) A multidisciplinary team is essential to coordinate this effort as hospital management, chief operating officer, chief medical officer, facility management and health directorate should be involved.
ii) The outpatient clinic should be reduced in terms of capacity to allow patients to maintain at least a 1mt distance between patients in the waiting room. Whenever possible, patients with severe liver disease should avoid social contacts, virtual clinics should be implemented and non-urgent visits should be postponed. Blood tests and imaging if possible should be performed in medical centres not managing COVID-19 positive patients. In compensated liver disease drugs can be dispensed as required and telemedicine consultation is advisable and encouraged. Hepatocellular carcinoma screening in cirrhotics must be maintained, while endoscopy sessions should be kept to a minimum by applying Baveno criteria whenever possible (21).
iii) Measures to avoid viral spread in emergency endoscopy units have been described elsewhere and should be implemented (22).
iv) In case the appointment cannot be postponed, for protection of patients and healthcare professionals, screening of all patients before entering the outpatient clinics is mandatory, asking for their epidemiology history in the past 14 days, and any related symptoms. Surgical facemask should be given to all patients and hand

washing is required. If possible, accompanying visitors of adult patients should not be allowed.

v) If COVID-19 cannot be excluded, patients should be allocated to an independent area to screen for COVID-19 including routine whole blood test, chest imaging, CRP, influenza A+B and COVID-19 nucleic acid test for selected patients. All suspected or confirmed cases who met COVID-19 management guideline, should be hospitalized in an independent building dedicated to COVID-19 patients. The liver specialist will work together with the medical staff in this independent building and take care of liver patients with suspected or confirmed COVID-19.

vi) If COVID-19 can be excluded, patients can be allocated to outpatient clinics as usual. Physicians should wear a surgical mask during the visit and routinely wash their hands or change gloves after every physical examination.

vii) Liver specialists should create separated teams, with one team managing COVID-19 negative patients also managing the outpatient clinic and another team managing COVID-19 suspected or confirmed patients. Table 1 summarizes the recommendations on which visits/procedures should be maintained.

Unmet clinical needs and main research questions

Several questions about liver injury in patients with COVID-19 and the role of the liver in the pathogenesis of COVID-19 need to be answered. Among the most prominent (highlighted in Figure 1):

a) What is the frequency and pathogenesis of liver injury during COVID-19, which are the risk factors, and how to differentiate the liver injury due to different etiology? What is the evolution of liver damage after the resolution of infection?

b) Does SARS-CoV-2 directly infect the liver? Do liver cells secrete infective viral particles? Is there any possible role for biliary shedding of the virus in facilitating infection of intestinal cells (also expressing ACE2) fecal-oral transmission (23)?

c) Which is the incidence of DILI during the treatment of COVID-19? Which drugs are at higher risk?

d) Are the patients with pre-existing liver disease more susceptible to COVID-19? Is there a modifying effect of immunosuppression (which might even be associated with protection against severe COVID-19) or disease severity? Is the severity of the underlying liver disease a prognostic factor? Is there any risk of liver decompensation in patients with severe pre-existing liver disease? Collaborative research registries endorsed by major scientific societies will be particularly useful to answer this question.

e) Is there an independent prognostic role of liver damage on COVID-19 prognosis? Does liver involvement play a causal role in disease pathogenesis by altering the secretion of cytokines, coagulation factors (given the prothrombotic state of severe COVID-19 (24, 25)) and other mediators?

Liver International against COVID-19

Liver International will not miss the opportunity to support hepatologist and liver researchers in fighting and finally stopping the pandemic. We have several associate editors who are both experts in liver disease as well as in infectious diseases, with direct clinical and research experience in the field. Therefore, Authors are encouraged to submit high quality scientific manuscripts regarding COVID-19. The turnaround time will be less than 1 week. We guarantee

to provide free-access for all accepted papers related with COVID-19, which will be highlighted in a special section in the website (8).

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FIGURE LEGENDS

Figure 1. SARS-CoV-2 infection and the liver. GI: gastrointestinal; IL-6: interleukin-6.

TABLES

Table 1. Recommendations for the management of liver disease outpatient clinic during the COVID-19 epidemic.

	Chronic hepatitis (viral & others)	Autoimmune and cholestatic disorders	Cirrhosis	HCC	Transplant
F2F clinic	Postpone monitoring for NASH, HCV, HBV	Postpone monitoring for PBC, PSC	Yes	Yes	Yes
Virtual clinics	Yes (AEs)	Yes	Yes (weight, symptoms)	Yes (AEs)	Yes (AEs)
Dispense drugs though territorial pharmacy	Yes	Yes	Yes	Yes	Yes
Treatment	Start pharmacological treatment only when urgent	Start immunosuppression when needed	Do not change routine practice	Start drug treatment when needed	Relevant decrease in donor availability
Invasive procedures and surgery	Avoid liver biopsy	Avoid liver biopsy	Maintain slots for invasive procedures in COVID-19-free facility	Reduce surgery (lack of ICU)	Maintain slots for invasive procedures in COVID-19-free facility
Diagnostics			HCC surveillance in COVID-19-free hospital	HCC monitoring in COVID-19-free hospital	
Special indications				Continue HCC board meetings	

AEs: adverse events; F2F: face-to-face; HBV: hepatitis B chronic virus infection, HCC: hepatocellular carcinoma; HCV: hepatitis C chronic virus infection, ICU: intensive care unit, NASH: nonalcoholic steatohepatitis.