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Coronavirus Disease 2019-Liver Injury-Literature Review and Guidelines Based on the Recommendations of Hepatological Societies

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

The aim of our paper was to present current knowledge, review literature and available practice guidelines of international hepatological associations regarding the effect of severe acute respiratory syndrome coronavirus 2 coronavirus on the liver, patients with underline liver disease, awaiting on liver transplantation (LTx) or being after LTx in the pandemic coronavirus disease 2019 area.

Keywords: Severe acute respiratory syndrome coronavirus 2; Coronavirus disease 2019; Liver; European Association for the Study of the Liver-European Society of Microbiology and Infection Diseases, American Association for the Study of Liver Diseases recommendation

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by Severe respiratory syndrome cornoavirus 2 (SARS-CoV-2). Clinical presentation includes fever, non-productive cough, dyspnoea, and in severe cases, respiratory failure [1-3]. Other, rarely observed symptoms include fatigue, loss of appetite, sneezing, runny nose, sore throat, anosmia, muscle and/or abdominal pain. Gastrointestinal symptoms such as nausea, vomiting and diarrhoea or elevated activity of liver enzymes have been observed in varying percentages of patients [1-3]. While in the majority of cases course of the infection is mild, in some patients the disease may progress to pneumonia, acute respiratory distress syndrome, multiorgan dysfunction such as renal-, heart- or liver injury. The time from exposure to onset of symptoms range from two to fourteen days (typically four-five days). The virus is primarily spread among people through close contact, often via small droplets produced by coughing, sneezing or talking. People may also become infected by touching a contaminated surface and then touching their eyes, nose or mouth. SARS-CoV-2 has been detected in the stool. Therefore, fecal-oral route of virus transmission is also possible [1-3].

SARS-CoV-2 is a positive-sense single-stranded RNA virus and belongs to the broad family of viruses known as coronaviruses. Like other coronaviruses, SARS-CoV-2 has four structural proteins:spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. The spike

protein enables the virus to attach to and fuse with the membrane of a host cell. Several protein modelling studies on the SARS-Co-V spike protein have shown sufficient affinity of the virus to the angiotensin converting enzyme 2 receptor (ACE2) on human cells. Recent studies showed that ACE2 receptor mediates the cell entry of SARS-CoV-2. ACE2 receptor is mostly expressed in the lungs, heart, kidneys, and intestine and was found to be expressed on endothelial cells of bile duct cells and the liver, which makes the liver a potential target for SARS-CoV-2 [2].

PATHOMECHANISM OF LIVER INJURY

The pathomechanism of liver damage in patients with COVID-19 is probably caused by several factors [1-3]. Elevated transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) and/or gammaglutamyltransferase (GGT) activity might be associated with hyperactivated immune responses and "cytokine storm", systemic inflammation, severe hypoxemia and acute respiratory failure (especially in the critical phase), septic shock, multiple organ dysfunction or failure, intestinal endotoxemia, drug toxicity and progression of pre-existing liver diseases [4-16]. The mechanism of liver injury during SARS-CoV-2 infection suggests that it may infect the bile duct cells (biliary cells have high expression of ACE2 receptor) and cause the abnormal liver function in selected patients. The data concerning morphological abnormalities in the liver in patients with COVID-19 are scarce [17-19]. Authopsy showed moderate microvascular steatosis and mild lobular and portal activity in the liver as well as centrilobular sinusoidal dilation or patchy necrosis in selected cases [17-19].

Table 1 [4-16] summarizes studies reporting liver injury SARS-CoV-2 adult patients infection. The presented data confirm that liver injury is more prevalent in severe cases of COVID-19 in comparison to milder ones.

Hepatologists and liver transplantologists from all over the word face a challenge how to deal with patients with various liver diseases or after liver transplantation (LTx) in pandemic era of COVID-19. Fortunately, experts from international societies have developed practical guidelines and clinical recommendations that are briefly summarized below.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER-EUROPEAN SOCIETY OF MICROBIOLOGY AND INFECTION DISEASES RECOMMENDATION

Recently, European Association for the Study of the Liver (EASL) and European Society of Microbiology and Infection Diseases (ESMID) have published a position paper with a recommendation for patients with liver diseases during COVID-19 pandemic [17]. It is unclear if chronic liver diseases should be considered as risk factors of severe course of COVID-19 due to a small number of appropriate studies. All patients with chronic liver diseases should adhere to common rules of physical distancing. Patients with compensated as well as with decompensated liver disease should use telemedicine or visits by phone wherever possible, routine laboratory testing can be performed locally/off-site and they should be informed about the importance of vaccination against Streptococcus pneumonia and influenza. Particular considerations should be given to patients with non-alcoholic

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Table 1. Papers evaluating liver function in adult patients infected with SARS-CoV-2

Author	Patient number	Abnormal value of laboratory result				Comments
		ALT, AST, LDH U/L – elevated	PT increased	Albumin deceased	Total bilirubin increased	
Chen et al. [4]	99	ALT 28 (28.3), AST 35 (35.4), LDH 75 (75.8)	5 (5.1)	97 (98.0)	18 (18.2)	(only in one pts AST-1,445 U/L, ALT-7,590 U/L)
Huang et al. [5]	41	AST 15 (36.6), LDH 29/40 (72.5)	-	-	-	Elevated: AST "ICU care" 8/13 (61.5), AST "no ICU care" 7/28 (25.0), median PT 12.2 s [IQR 11.2–13.4]; higher than "non-ICU patients" (median PT 10.7 s [9.8–12.1], p=0.012)
Wu et al. [6]	80	ALT 3 (3.8), AST 3 (3.8), LDH 17 (21.3)	-	2 (2.5)	1 (1.23)	No pts with increased PT
Xu et al. [7]	62	AST 10 (16.1), LDH 17 (27.4)	-	-	-	
Wang et al. [8]	138	Significantly higher ALT AST, LDH in "ICU cases" (maximum value: ALT 57 U/L, AST 70 U/L, LDH-596 U/L)	-	-	Significantly higher total bilirubin (max value 18.6 μmoL/L)	
Shi et al. [9]	81	AST 43 (53.1)	-	-	-	7 (8.6) had hepatitis or liver cirrhosis in anamnesis
Yang et al. [10]	52	Liver dysfunction 15 (28.8) - all critically ill adult patients	12.9% in non-survivors	-	-	Liver dysfunction: survivors (n=20) 6 pts (30.0) non-survivors (n=32) 9 pts (28.1)
Mo et al. [11]	155	Significantly higher AST (max 65 U/L), LDH (max 437 U/L) in refractory cases	-	Significantly lower albumin (min. 32 g/L) in refractory cases	-	On admission total chronic liver disease 7 (4.5)
Zhou et al. [12]	191	ALT 59/189 (31.2), LDH 123/184 (66.8)	11/182 (6.0)	Significantly lower albumin in "non-survivors" 29.1 g/L (26.5–31.3)	-	Abnormal ALT: "survivors" 24% vs. "non-survivors" 48% Abnormal LDH: "survivors" 54% vs. "non-survivors" 98% coagulopathy 37 (19.4)
Guan et al. [13]	1,099	ALT 158/741 (21.3), AST 168/757 (22.2), LDH 277/675 (41.0)	-	-	76/722 (10.5)	HBV infection in 23 pts (2.1)
Xie et al. [14]	79	ALT 25 (31.6), AST 28 (35.4)	-	-	5.1%	Median value of ALT, AST and bilirubin for entire cohort was 36.5 (17.5–71.5) U/L, 34.5 (25.3–55.3) U/L and 12.7 (8.1–15.4) mmoL/L respectively
Fan et al. [15]	148	ALT 27 (18.2), AST 32 (21.6)	-	-	9 (6%)	55 pts (37.2) had abnormal liver function at hospital admission; abnormal GGT 26 (17.6), and ALP 6 (4.1).
Singh and Khan [16]	250	ALT 60/130 (46.2), AST 80/130 (61.5)	-	-	(>2 mg/dL) 30/120 (25.0)	Patient with pre-existing liver disease: abnormal GGT-10/10 (100.0)
	2,530	ALT 390/770 (50.6), AST 520/770 (67.5)	-	-	(>2 mg/dL) 70/770 (9.1)	Patient without pre-existing liver disease: abnormal GGT-20/30 (66.7)

Values are presented as number (%).
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, ICU: intensive care unit, PT: prothrombin time, HBV: hepatitis B virus, GGT: gamma glutamyl transpeptidase.
Due to the different range for ALT, AST, LDH, PT, GGT and total bilirubin in the centers the statements "elevated" or "decreased" were used in relation to local laboratory standards (normal range).

fatty liver disease (NAFLD)/non-alcoholic steatohepatitis who may suffer from diabetes and hypertension putting them at increased risk of a severe course of COVID-19. In the group of patients with autoimmune liver disease reducing immunosuppressive therapy is not recommended. Patients with viral hepatitis (hepatitis C virus [HCV], hepatitis B virus [HBV]) have no increased risk of a severe SARS-CoV-2 infection. In patients with compensated cirrhosis screening for varices by esophagogastroscopy should be reserved for patients at risk of variceal bleeding and non-invasive risk assessment (thrombocyte count, Baveno VI) for the presence of varices should be applied for patient's stratification. Liver biopsy should be deferred in patients without COVID-19 but with chronic viral hepatitis, NAFLD and in cases with mildly elevated transaminases of unknown origin but this medical procedure should be performed in patients with high activity of ALT of an unknown origin (e.g., >5× upper limit of normal [UNL]) or with liver masses suspicious of malignancy. In the case of COVID-19 liver biopsy should be deferred in most patients.

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Liver transplants should be performed only in patients with poor short-term prognosis acute/acute-on-chronic liver failure, high score of model for end-stage liver disease/ pediatric end-stage liver disease (MELD/PELD) or/and exceptional MELDs/PELDs scores and hepatocellular carcinoma (HCC) at the upper limits of the Milan criteria. Patient's evaluation before LTx should be minimized to shorten hospital stay. Intensive treatment of all possible complications of liver cirrhosis is recommended (to avoid admission to hospital).

It is recommended that SARS-CoV-2 testing should be performed in patients with acute decompensation or acute-on-chronic liver failure as well as pre-transplantation for both donors and recipients (assuming that negative testing does not exclude potential infection).

In patients with HCC continue systematic treatment is recommended as well contact with medical staff by telemedicine/phone to consider potential indications for LTx.

In stable liver transplant patients, it is recommended to perform local laboratory tests (including drug level) and follow-up visit by telemedicine or phone.

At the outpatient care the remodeling of waiting areas to allow sufficient distances between patients as well as reduction of waiting time and encouraging patient to wait outside should be considered. The exposure to medical staff should be minimized.

It is not recommended to reduce immunosuppressive therapy during a COVID-19 pandemic, and where necessary only after consultation with a specialist. Vaccination for Streptococcus pneumoniae and influenza are recommended for patient with chronic liver disease as well as after LTx.

Very important issue in the EASL-ESMID recommendation is discussion on selected repurposed drugs that have been suggested for the treatment of COVID-19 in context to its use in patients with liver disease or after liver transplantation. Lopinavir/ritonavir had well known interactions with immunosuppressive drugs and current evidence does not support their administration in the treatment of COVID-19.

General recommendations for patients with chronic liver disease and COVID-19 is to avoid acetaminophen overdose (maximum 2–3 g/day). In patients with cirrhosis and portal hypertension non-steroidal anti-inflammatory drugs are not recommended. For patients with chronic liver disease and COVID-19, specific liver-related diagnostic (e.g., ultrasonography, liver biopsy) procedures are described in the article.

THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES RECOMMENDATIONS

The American Association for the Study of Liver Diseases (AASLD) presented its position on practical hepatological issues during the COVID-19 pandemic [18] and provided some recommendations. Similarly to EASL-ESMID recommendation it was noted that patient with NAFLD may be at higher risk for severe COVID but it is unclear if the risk is specific to NAFLD or to coexisting metabolic risk factors.

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Due to insufficient data, patients with cirrhosis and patients on immunosuppressant therapy (autoimmune hepatitis [AIH], after LTx) should be considered to be at increased risk for severe COVID-19. Imaging examinations as ultrasound or magnetic resonance imaging/ magnetic resonance cholangiopancreatography (MRI/MRCP) should be avoided unless it might influence process of decision-making in further therapy.

Most follow-up visits should be organized using telemedicine or phone system. Consultations in doctor's office should be restricted to new patients with urgent problems and clinically significant liver disease (e.g., jaundice, ALT or AST >500 U/L, recent onset of hepatic decompensation). It is advised patient not to travel during the COVID-19 pandemics.

The authors emphasizes that abnormal liver biochemical parameters should not be a contraindication to investigational or off-label drugs for COVID-19, although AST or ALT >5× ULN may exclude patients from some investigational therapies.

Patients who are treated with direct-acting antiviral drugs against HBV or HCV should continue therapy. Initializing of therapy in patients with HCV infection may be delayed but this does not apply to patients with HBV infection and clinical suspicion of a hepatitis B flare.

In patients with HCC examination can be safely postponed for two months (doubling time for HCC is 4 to 6 months). Liver ultrasound or liver biopsy procedures may be postponed with exception of urgent cases. Immunosuppressive treatment in patients with liver disease e.g., in AIH or after liver transplantation (including treatment of graft rejection) should be continue according to the normal schedule. A negative SARS-CoV-2 result of donor testing must be obtained prior to transplantation. Urgent liver transplantation must not be delayed.

Separate recommendations apply to patients receiving COVID-19 immunosuppressive therapy. In these group it is recommended to minimize the high dose of prednisone and consider reduction of azathioprine or mycophenolate, especially in the case of lymphopenia, fever or severe pneumonia in the course of COVID-19.

The authors state that reduction of organ donation is expected which may have a significant negative impact for the transplant waiting list. They recommend a suspending of donor liver transplant program and its restriction only for patients with acute liver failure. The recommendations of both EASL-ESMID and AASLD are consistent, complement each other and give good guidance to hepatologists during the COVID-19 pandemic.

The AASLD guidelines point out that COVID-19 is rare in children and the course of the disease is rather mild in most of them. In rare pediatric cases with severe COVID-19 elevated ALT or AST are seen, but if it is present, their values are slightly above ULN.

The AASLD recommendation is to evaluate all children with elevated AST or ALT for underlying liver diseases and other coexisting infections, as COVID-19 is not commonly associated with abnormal liver biochemical parameters in children.

The impact of SARS-CoV-2 infection on children is probably mild in the majority of cases. There are only a few papers evaluating liver function in children infected with SARS-CoV-2 (**Table 2**) [19-22].

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Table 2. Papers evaluating liver function in children infected with SARS-CoV-2

Author	Number of infected children	Number of children with elevated ALT
Sun et al. [19]	8	4 (50.0)
Ma et al. [20]	115	11 (9.6)
Qui et al. [21]	36	2 (5.6)
Lu et al. [22]	171	21 (12.3)

Values are presented as number only or number (%).
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, ALT: alanine aminotransferase.

Therefore, according to European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), the risk of late diagnosis or deferring treatment of gut and liver disorders in childhood outweighs in the majority of patients risk associated with COVID-19.

INTERNATIONAL PEDIATRIC TRANSPLANT ASSOCIATION RECOMMENDATION

International Pediatric Transplant Association (IPTA) provides update of guidelines for transplant clinicians every few weeks. It is underlined that deceased donors with unexplained respiratory failure leading to death as well as persons who returned from countries with >10 infected patients or who have been exposed to a patient with confirmed or suspected COVID-19 within 14 days should be excluded from donation.

To minimize the risk of false positive testing and organ wastage routine testing of upper and lower airway specimens by PCR/NAT should be recommended in areas with significant ongoing community transmission and in donors with suspicion of COVID-19 positivity. However, national guidelines may recommend routine testing of donors for SARS-CoV-2.

Temporary suspension of the deceased donor program should be considered in a country with widespread community transmission.

CONCLUSION

1. The pathomechanism of liver damage in COVID-19 is unclear and need further studies.
2. There is a possibility of increased risk of abnormal liver function in patients with severe course of COVID-19.
3. For patients with a pre-existing history of liver diseases (especially older patients), special attention should be paid to monitoring hepatic changes caused by COVID-19.
4. Patients with advanced liver disease and after liver transplantation are at risk of infection with SARS-CoV-2 and severe course of COVID-19.
5. COVID-19 pandemic requires unusual care, which may have a negative impact on the care of patients with chronic liver disease.
6. Liver damage in mild cases of COVID-19 is often transient and can recover without any special treatment.
7. Prevention of hospital spread of the virus (patients, staff), maintaining a good standard of care for patients requiring immediate medical assistance, and medical counseling in the form of telemedicine are real challenges for hepatologists in the era of COVID-19 pandemic.

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