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Impact of COVID-19 on the care of patients with liver disease: EASL-ESCMID position paper after 6 months of the pandemic

Two leading medical societies for liver disease and infectious diseases, EASL and ESCMID, have reviewed evidence from the published studies on the impact of COVID-19 on patients with liver disease and the possible influence of chronic liver disease on the course of COVID-19. Published 04 August 2020, the follow-up report to their first paper now answers five questions:

- **What are the risks of COVID-19 infection and its severity for people with chronic liver disease?**
- **What is the impact of COVID-19 on the liver?**
- **How should people with liver disease be cared for during the COVID-19 outbreak?**
- **Which procedures can go ahead/be delayed?**
- **What is known about COVID-19 treatments and the liver?**

What are the risks of COVID-19 infection and its severity for people with chronic liver disease?

Overall, because only one person out of every hundred reported cases of COVID-19 had liver disease, it is thought that having chronic liver disease itself does not put someone at higher risk of becoming infected with SARS-CoV-2 (the virus that causes COVID-19) or getting a more severe COVID-19 than the average person.

However, people with more advanced liver disease are at higher risk, as are some people with particular liver conditions.

What is chronic liver disease?
Chronic liver disease describes a liver disease that lasts a long time. Examples include hepatitis B, hepatitis C, autoimmune liver diseases, and fatty liver disease (NAFLD).

Advanced liver disease (cirrhosis)

Cirrhosis is scarring of the liver over a long time due to specific causes. Decompensated cirrhosis means the individuals experience complications of their liver disease such as a build-up of fluid in the body, gastrointestinal bleeding and mental disturbances. **People who have cirrhosis, regardless of their underlying chronic liver disease, are not at a higher risk of becoming infected with SARS-CoV-2 but are at higher risk of getting severe COVID-19, even more so if they have decompensated cirrhosis.**

What is decompensated cirrhosis?

Decompensated cirrhosis occurs when there is extensive scarring in the liver, and the liver is unable to function properly. It is sometimes called 'hepatic decompensation'.

Decompensated cirrhosis leads to complications such as a build-up of fluid in the body (ascites), gastrointestinal bleeding (GI bleeds) and mental disturbances (hepatic encephalopathy).

Non-alcohol related fatty liver disease (NAFLD)

NAFLD includes the spectrum of conditions from fatty liver to NASH (non-alcohol related steatohepatitis). **Some people with NAFLD are at risk of having a more severe course of COVID-19.** It is not clear yet whether this is because of NAFLD itself, or because of factors that are associated with NAFLD, such as obesity (particularly in men), high blood pressure and diabetes.

Viral hepatitis

Chronic viral hepatitis includes hepatitis B (HBV), hepatitis C (HCV), hepatitis D (HDV) and hepatitis E (HEV). **There has been no strong evidence to indicate that chronic viral hepatitis affects the severity of COVID-19. Experts advise against stopping treatments for chronic hepatitis B and C.**

Autoimmune hepatitis (AIH)

To date, there has been **no strong evidence to indicate that autoimmune hepatitis itself affects the risk of SARS-CoV-2 infection and severity of COVID-19**. The treatments for AIH (corticosteroids and immunosuppression therapy) *may* be associated with a more severe COVID-19 disease course, but there are very real risks to the patient if they do not take their prescribed AIH medications properly. **Experts advise against stopping or reducing AIH treatments** but acknowledge that more research is needed to fully understand all the risks.

Liver transplantation

Reports about COVID-19 risk and severity in liver transplant patients across the world vary. EASL-ESCMID say that the **available data *overall* does not support the concern at the beginning of the outbreak that there is a higher risk of severe COVID-19 in people who have had a transplant**. However, other issues such as a history of cancer may increase the risk of more severe COVID-19.

What is the impact of COVID-19 on the liver?

Changes to liver blood test results have been reported in patients with COVID-19 who have liver disease and also in those who do not have liver disease, particularly in patients admitted to hospital. It is not known if this is a direct effect of the SARS-CoV-2 virus, or if this is a result of the COVID-19 attack on the body or even the drugs used to treat it. Studies are ongoing to investigate the processes involved, and it is not yet fully understood what these liver changes mean for patients who get COVID-19.

How should people with liver disease be cared for during the COVID-19 outbreak?

Healthcare systems across the world have adapted to manage COVID-19 patients. This has affected and continues to affect healthcare for non-COVID-19 patients, including those needing liver services. For people with chronic liver disease, this means that routine appointments may be delayed, telemedicine may replace some face-to-face appointments, and laboratory tests and procedures may be delayed, cancelled or carried out in a different place (for example at general practitioners instead of your usual hospital).

A serious knock-on effect of not receiving the usual care is that patient health gets worse: liver disease can progress untreated, people do not get diagnosed quickly enough, and liver cancers are not detected as quickly as usual. In turn, we know people with more advanced liver disease are at increased risk of severe COVID-19. To avoid a vicious cycle of liver disease and COVID-19, and to maintain the health and wellbeing of people with liver disease, EASL-ESCMID urges healthcare professionals and hospitals to tackle these challenges and aim to provide high quality care through:

1. Continuing to use new technologies and ideas that worked well during the outbreak such as telemedicine when appropriate and using local services for monitoring disease progression.
2. Restarting clinical trials.
3. Carefully prioritising patients in an informed way for care, procedures and treatments when resources are limited, balancing the risk of SARS-CoV-2 infection and individual patient needs.

EASL-ESCMID's vision is a return to gold standard liver disease care as soon as possible, with timely diagnosis, treatment and surveillance, ongoing patient education, and early intervention for high-risk patients with COVID-19.

EASL-ESCMID RECOMMENDATIONS

All liver disease patients

EASL-ESCMID recommend that all liver disease patients who need to be admitted into hospital should have a PCR test before admission.

Patients with cirrhosis

EASL-ESCMID recommend that your healthcare team:

- is mindful that patients (with any chronic liver disease) who have cirrhosis are vulnerable to impact of SARS-CoV-2 infection and are at high risk of new or worsening liver decompensation, severe COVID-19 or death.
- is mindful that patients (with any chronic liver disease) who have cirrhosis are vulnerable to delays or changes to healthcare during the COVID-19 outbreak.
- follows clinical practice guidelines for patients with cirrhosis where possible and provides care of the highest standard.
- prioritises SARS-CoV-2 testing in patients with worsening hepatic decompensation (advanced cirrhosis) or ACLF (acute-on-chronic liver failure, where a patient with advanced cirrhosis gets worse and other organs start to fail), even if there are no respiratory symptoms present.
- manages non-COVID-19 patients with cirrhosis who need to stay in hospital in a non-COVID-19 ward, preferably in a side room. This is to try to minimise the risk of SARS-CoV-2 infection within the hospital setting.
- follows guidelines closely to reduce your risk of spontaneous bacterial peritonitis (SBP), gastrointestinal haemorrhage (GI bleed) and hepatic encephalopathy (HE). These are complications of advanced cirrhosis that might require a hospital stay.
- admits you to hospital early if you become infected with SARS-CoV-2.
- is cautious about using vasoconstrictor therapy in patients with cirrhosis and COVID-19.
- considers a symptoms-based approach (using palliative care guidelines) to make patients with advanced liver disease and COVID-19, who deteriorate very quickly, more comfortable.
- advises you to have a vaccination for *Streptococcus pneumoniae* and influenza.

NAFLD patients

EASL-ESCMID recommend that your healthcare team:

- talks to you about diet and physical activity, especially managing this during lockdown periods (and the potential impact of social isolation).
- provides nutritional guidance, weight loss advice and diabetes management if appropriate to help reduce the risk of you getting a more severe course of COVID-19.
- admits you to hospital early if you become infected with SARS-CoV-2.

Viral hepatitis patients

EASL-ESCMID recommend that your healthcare team:

- continues your HCV and HBV treatment (if you are being treated).
- uses telemedicine for routine appointments and local facilities for tests where possible.

- sends follow-up medication to you by post to help ensure you complete the full treatment course.
- follows the current guidelines for the treatment and management of HBV and HCV if you do not have COVID-19. If you have COVID-19, your hepatitis treatment will be started after you recover from COVID-19.
- decides on case-by-case basis for HBV treatment in patients with COVID-19 and severe HBV infection.
- considers alternative treatments for HBV during the COVID-19 outbreak because the impact of interferon alpha is not yet fully understood.
- considers the use of antiviral therapy to prevent viral flare or reactivation in patients with COVID-19 who have or have had HBV and are receiving corticosteroids, tocilizumab or other immunosuppressive therapies.
- continues to work towards the World Health Organisation goal of elimination of viral hepatitis by 2030 and adapts to meet the challenges of COVID-19.

Alcohol-related liver disease patients

EASL-ESCMID recommend that your healthcare team:

- talks to you about alcohol consumption, especially during lockdown periods (and potential for social isolation and its effects).
- adapts alcohol services so they are always available and accessible for you during the COVID-19 outbreak.
- carefully considers the risks and benefits of prescribing corticosteroids for patients with severe alcoholic hepatitis.
- answers your questions about alcohol and SARS-CoV-2. This is important because there are some myths circulating online that could lead to dangerous behaviours. It is important to check with your doctor if you are not sure about anything you find out from a non-medical source relating to COVID and alcohol.

Autoimmune liver disease patients

EASL-ESCMID recommend that your healthcare team:

- does not reduce any immunosuppressive medication you are taking except in special circumstances such as medication-induced lymphopenia, or bacterial/fungal superinfection in cases of severe COVID-19, and only after checking with a specialist.
- considers budesonide instead of corticosteroids as a first-line therapy if you are diagnosed with autoimmune hepatitis (AIH) (and no cirrhosis) during the COVID-19 outbreak. This is because of concerns that people taking higher doses of corticosteroids may increase the risk of SARS-CoV-2 infection and increase the risk of a more severe course of COVID-19.
- reviews your corticosteroid dose (if you are taking them and develop COVID-19) to avoid adrenal insufficiency. EASL-ESCMID recommend ***not*** adding or switching to dexamethasone unless you need support to breathe in hospital.
- advises you to have a vaccination for *Streptococcus pneumoniae* and influenza.
- is aware that as yet there are no specific recommendations for patients with primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC) or IgG4-related disease.

Patients who need a liver transplant

Patients with decompensated cirrhosis who are on the waiting list for a transplant are at high risk of severe COVID-19 and death.

EASL-ESCMID urges liver transplant centres to maintain liver transplant services during the COVID-19 outbreak wherever possible, or restore these services as soon as possible if they are temporarily shut down. Where there are limited resources, patients at greatest risk of death without a transplant should be prioritised.

EASL-ESCMID recommend that:

- all donors are tested for SARS-CoV-2 (by a PCR test performed in a naso-pharyngeal swab) and if infected, their livers are **not** used for transplantation. This is because scientists do not yet understand the risks of transmission to you through a liver transplant.
- national and local strategies are put in place to make available, select and allocate donor livers that include checking medical history, chest imaging and COVID-19 status.
- measures are put in place to reduce the risk of SARS-CoV-2 infection for patients at all stages of the transplant journey, including the time that they are assessed for suitability for transplantation. In areas with a high COVID-19 burden, measures include strict social isolation for patients on the waiting list, telephone screening and the use of strictly COVID-19 free hospital zones for pre- and post-transplant care.
- your healthcare team should talk to you about the risks associated with COVID-19 and transplantation and what they are doing to minimise them.
- your healthcare team considers living-donor liver transplants carefully on a case-by-case basis during the COVID-19 outbreak.

People who have had a liver transplant

EASL-ESCMID recommend that your healthcare team:

- does not reduce any immunosuppressive medication you are taking to help prevent SARS-CoV-2 infection, except in special circumstances such as medication-induced lymphopenia, or bacterial/fungal superinfection in cases of severe COVID-19, and only after checking with a specialist.
- is mindful that some transplant recipients may be anxious about COVID-19 and this may affect their willingness to attend appointments or follow medication instructions.
- closely monitors your blood tests for drug interactions if you have COVID-19 receive new or existing treatments.
- admits you to hospital early if you become infected with SARS-CoV-2.
- is mindful of risk factors that might lead to a more severe course of COVId-19. In liver transplant patients, these include cancers, frailty, problems with the way the new liver functions and metabolic syndrome (high blood pressure, diabetes and obesity).
- advise you to have a vaccination for *Streptococcus pneumoniae* and influenza.

Liver cancer patients

Liver cancer is referred to as HCC, which stands for hepatocellular carcinoma. The specific risk for people with HCC is not yet fully understood, but death from COVID-19 in patients with

cancer may be affected by age, sex and other conditions as opposed to cancer therapies. Patients with increased risk for HCC include those with high alpha-fetoprotein levels, advanced cirrhosis, chronic hepatitis B and hepatitis C and NASH/diabetes.
EASL-ESCMID recommend that your healthcare team:

- follows guidelines for the care of HCC including assessment for transplantation for suitable patients.
- uses multidisciplinary team meetings to advise on treatments. These can be held remotely.
- resumes full HCC surveillance where possible but if there are limited resources, to prioritise those patients at increased risk for HCC.

Which procedures can go ahead/be delayed?

Some procedures carry a risk of SARS-CoV-2 transmission.

Endoscopy

Endoscopy is a term used to describe invasive procedures where a tube goes inside the body to look closely at specific areas, take tissue samples, and do other tasks such as widening bile ducts or inserting/removing stents. **SARS-CoV-2 can be transmitted during endoscopic procedures.**
EASL-ESCMID recommend that:

- all patients have a SARS-CoV-2 test before their procedure if possible.
- in patients who test negative and in areas where there is a low COVID-19 burden, **endoscopic procedures should not be delayed for varices screening and treatment, bile duct widening or stent replacement in patients with primary sclerosing cholangitis (PSC) or people who have had a liver transplant.**
- in patients who have COVID-19, endoscopic procedures should be limited to emergencies only. Such emergencies include bacterial cholangitis and GI bleeds.

Ultrasound

An ultrasound scan is a routine procedure to check for signs of liver cancer in patients with liver disease.
EASL-ESCMID recommend that:

- your healthcare team should only delay your ultrasound scan (for liver cancer screening) where resources for screening and/or treatment are limited, and they should prioritise those patients at increased risk for HCC.
- for patients who have COVID-19, screening for HCC can be delayed until the patient has recovered.

Liver biopsy

A liver biopsy is an invasive procedure where a needle is put into the liver and a tiny bit of the liver is removed. Liver biopsies are used to help diagnose some liver diseases and to assess how much damage there is in the liver.
EASL-ESCMID recommend that:

- in areas where there is a low COVID-19 burden, liver biopsies should go ahead following usual care guidelines.
- in areas where there is a high COVID-19 burden, or limited resources, patients who need liver biopsies should be prioritised if liver blood tests are very high for no clear reason, when transplant rejection is suspected and if cancer is suspected.
- for patients who have COVID-19, the risks and benefits of a liver biopsy need to be considered on a case-by-case basis.

What is known about COVID-19 treatments and the liver?

COVID-19 treatments include brand new drugs and drugs that are used to treat other conditions. THE EASL-ESCMID update reviews the treatments that have known effects on the liver and the way it works. If you have COVID-19, your medical team will evaluate if treatment is needed and should consider the impact (if known) of the treatment on your liver and its interaction with medicines that you already take. Currently some drugs have been used for severe COVID-19, such as remdesivir and corticosteroids. Among them, only remdesivir has been approved by medical agencies. There are several ongoing studies evaluating other potential drugs. The drugs reviewed in the EASL-ESCMID update are: remdesivir, tocilizumab, corticosteroids, and anticoagulation.

Based on: Boettler T, Marjot T, Newsome PN, Mondelli MU, Maticic M, Cordero E, Jalan R, Moreau R, Cornberg M, Berg T. Impact of COVID-19 on the care of patients with liver disease: EASL-ESCMID position paper after 6 months of the pandemic. JHEP Reports. 2020 Aug 4.