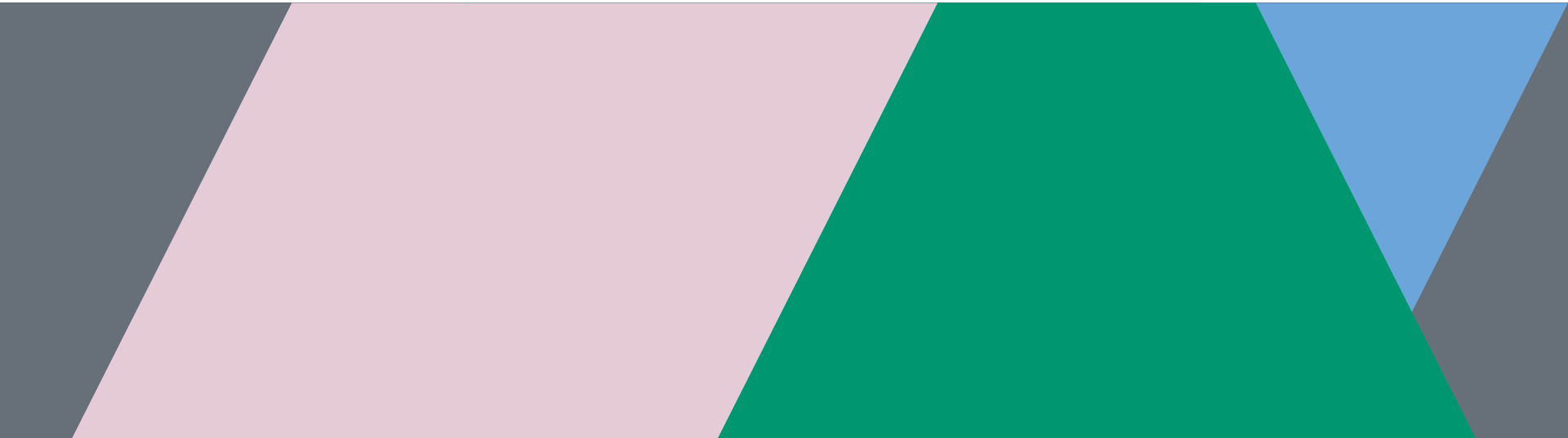
INSELGRUPPE

Journal Club Hepatology

26.11.2020 Lukas Balsiger



HEPATOLOGY

AASLD

SPECIAL ARTICLE | HEPATOLOGY, VOL. 72, NO. 1, 2020

Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement

Oren K. Fix,[1] Bilal Hameed,[2] Robert J. Fontana,[3] Ryan M. Kwok,[4] Brendan M. [illegible] Mulligan,[6] Daniel S. Pratt,[7] Mark W. Russo,[8] Michael L. Schilsky,[6] Elizabeth C. Verna,[9] Rohit Loomba,[10] [illegible] rge A. Bezerra,[12] K. Rajender Reddy,[13] and Raymond T. Chung[7]

+ Update 09.11.2020

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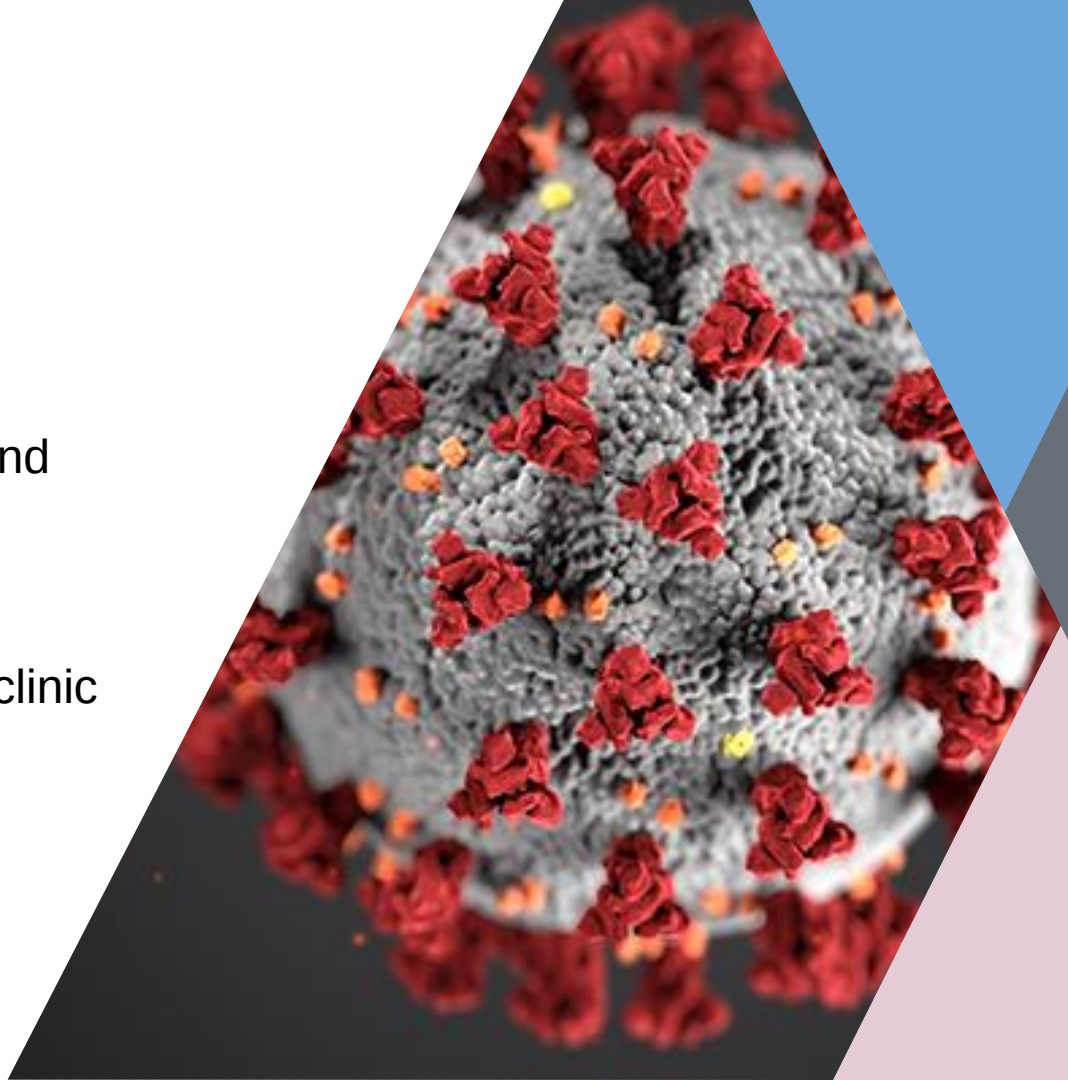
Goals

- Overview of AASLD recommendations and other resources
- Discussion on implications for our clinic



BMJ Journals

COVID-19

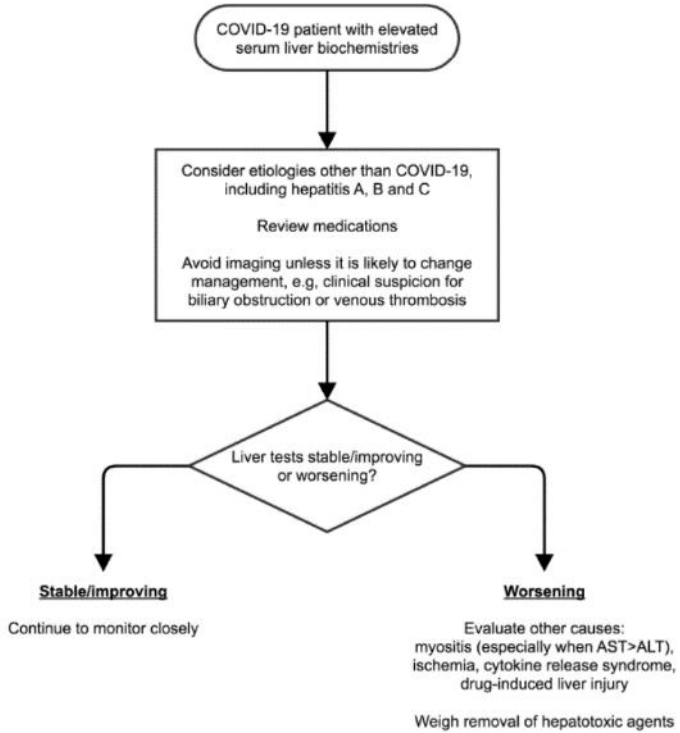
Gut

ORIGINAL RESEARCH

COVID-19 in an international European liver transplant recipient cohort

Chiara Becchetti ,[1] Marco Fabrizio Zambelli,[2] Luisa Pasulo,[3] Maria Francesca Donato,[4] Federica Invernizzi,[4] Olivier Detry,[5] Géraldine Dahlqvist,[6] Olga Ciccarelli,[7] Maria Cristina Morelli,[8] Montserrat Fraga,[9] Gianluca Svegliati-Baroni,[10,11] Hans van Vlierberghe,[12] Minneke J Coenraad,[13] Mario Cristobal Romero,[14] Andrea de Gottardi,[15] Pierluigi Toniutto,[16] Luca Del Prete,[2] Claudia Abbati,[2] Didier Samuel,[17] Jacques Pirenne,[18] Frederik Nevens,[19] Jean-François Dufour ,[1,20] COVID-LT group

COVID and serum liver biochemistries



Post- OLT	Cirrhosis	Viral hepatitis	HCC	Autoimmune hepatitis

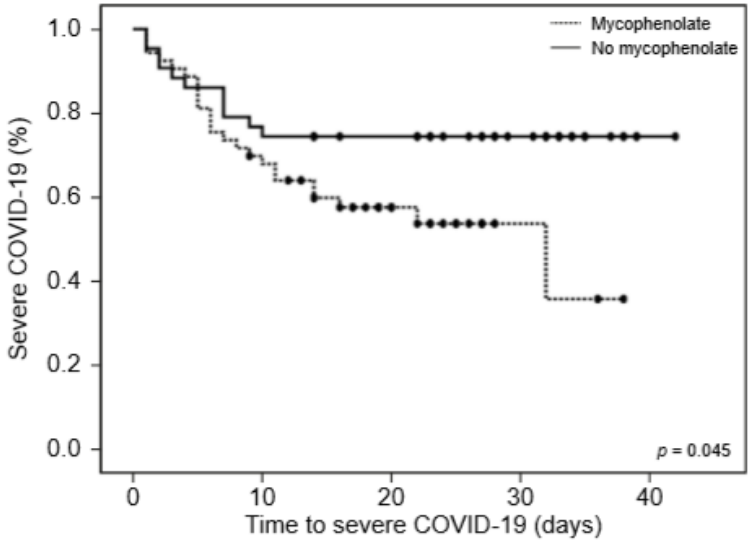
COVID and OLT

- Mortality not higher in OLT patients with COVID19
- Previous/active cancer = worse outcome
- More COVID cases in OLT patients but lower mortality

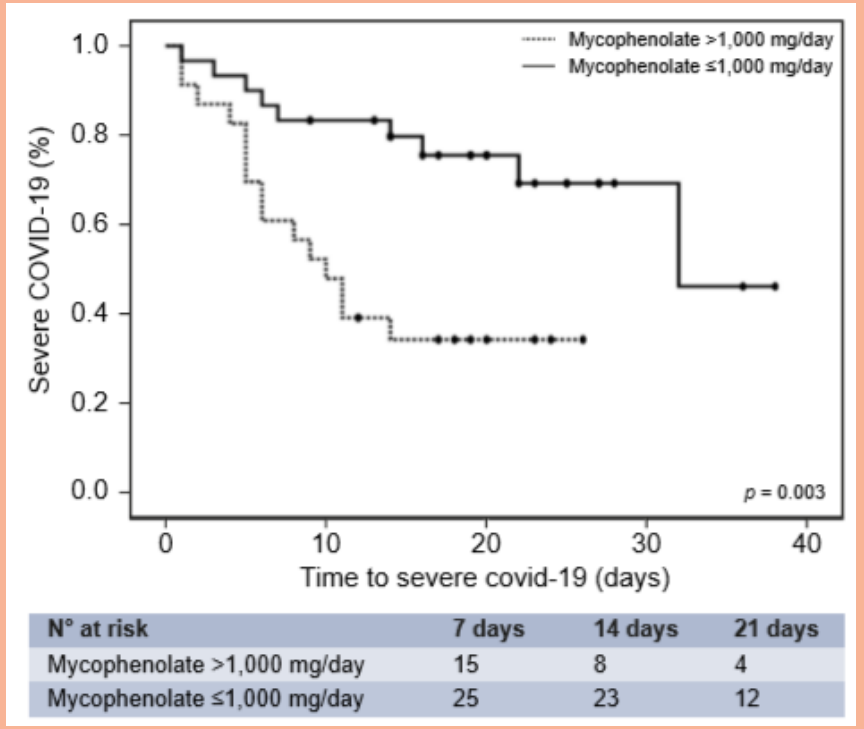
Becchetti C, Zambelli MF, Pasulo L, et al. Gut 2020;**69**:1832–1840.

Colmenero J, Rodríguez-Perálvarez M, Salcedo M, et al. Epidemiological pattern, incidence and outcomes of COVID-19 in liver transplant patients [published online ahead of print, 2020 Aug 1]. *J Hepatol*. 2020;S0168-8278(20)30521-3. doi:10.1016/j.jhep.2020.07.040

COVID and OLT



N° at risk	7 days	14 days	21 days
Mycophenolate	40	31	16
No mycophenolate	37	32	28



N° at risk	7 days	14 days	21 days
Mycophenolate >1,000 mg/day	15	8	4
Mycophenolate ≤1,000 mg/day	25	23	12

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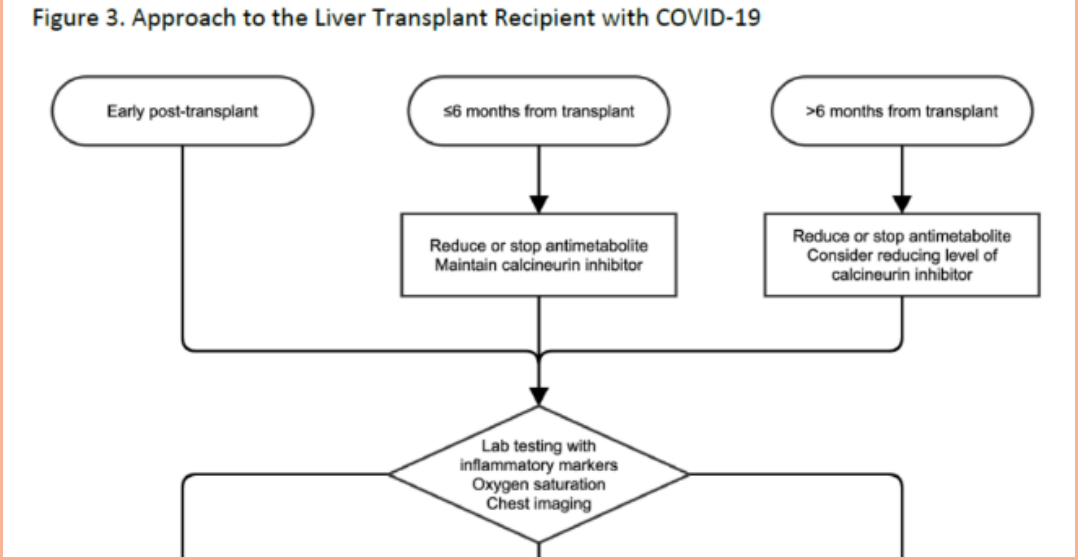
COVID and OLT

What is recommended (AASLD 09.11.2020)

- No changes in immunosuppression in patients w/o COVID



COVID and Cirrhosis

Table 2. Presentation of SARS-CoV-2 infection in 50 cirrhotic patients enrolled in the study.

Characteristics	Patients (n = 50)
Respiratory symptoms	
Cough	18 (36)
Shortness of breath/polypnea	21 (42)
Systemic signs and symptoms	
Fever	32 (64)
Fatigue	30 (60)
Acute hepatic encephalopathy	11 (22)
Myalgia/arthralgia	10 (20)
Diarrhoea	5 (10)
Acute kidney impairment	2 (4)
Headache	1 (2)
PaO_2/FiO_2, mmHg	
>400	14 (28)
>300-≤400	10 (20)
>200-≤300	12 (24)
>100-≤200	11 (22)
≤100	3 (6)
Suggestive features of COVID-19 pneumonia at imaging	
Chest radiography	22/37 (59)
Chest computed tomography	24/35 (69)
Blood tests	
Hepatitic flares[§]	6 (12)
Lactate dehydrogenase, U/L*	323 (267–408)
D-dimer, mg/L*	1,850 (1,092–4,232)
C-reactive protein, mg/dl	5 (3–15)
Ferritin, ng/ml	800 (404–1,567)

Table 3. Comparison of clinical and biochemical characteristics of cirrhotic patients at last visit* and at SARS-CoV-2 diagnosis.

Variables	Before COVID-19*	At COVID-19 diagnosis	p value
Albumin, g/dl	3.4 (3.2–3.9)	2.8 (2.6–3.2)	0.0003
Bilirubin, mg/dl	1.3 (0.8–2.8)	1.8 (0.8–3.8)	0.026
INR	1.2 (1.1–1.6)	1.3 (1.1–1.7)	0.042
Ascites	17 (34)	19 (38)	0.621
Encephalopathy	9 (18)	19 (38)	0.025
PLT			
count/mm^3	115,000 (76,500–159,250)	111,500 (61,000–171,750)	0.197
≤50,000/mm^3	7/44 (16)	11 (22)	0.425
WBC			
count/mm^3	4,500 (3,973–6,510)	5,680 (4,100–8,370)	0.559
≥10,000/mm^3	6/44 (14)	10/49 (20)	0.387
≤4,000/mm^3	11/44 (25)	11/49 (22)	0.773
Lymphocyte			
count/mm^3	1,157 (955–1,573)	995 (638–1,380)	0.067
≤1,500/mm^3	23/34 (68)	37/48 (77)	0.342
AST			
U/L	33 (25–68)	48 (35–87)	0.176
>40 U/L	15/43 (35)	32/48 (67)	0.002
ALT			
U/L	31 (24–51)	54 (24–85)	0.024
>40 U/L	18/45 (40)	29 (58)	0.003
Creatinine, mg/dl	1.0 (0.8–1.3)	1.1 (0.8–1.6)	0.007
Child-Pugh score:			0.05
A (5-6)	26 (52)	20 (40)	
B (7-9)	18 (36)	14 (28)	
C (10-15)	6 (12)	16 (33)	
MELD score	6 (6–9)	9 (6–15)	0.0003
MELD score ≥15	5 (10)	13 (26)	0.037

Values are reported as n (%) or median (IQR). Categorical variables have been compared using the χ^2 test, continuous variables have been compared using the Student's *t* test, all tests were 2-sided and used a significance level of 0.05.

*At last outpatient visit or at hospital admission (if SARS-CoV-2 diagnosed during hospitalization). °Last available outpatient visit or inpatients data before SARS-CoV-2 infection. ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; INR, international normalized ratio; MELD, model for end-stage liver disease; PLT, platelets; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; WBC, white blood cell.

Iavarone M, D'Ambrosio R, Soria A, et al. High rates of 30-day mortality in patients with cirrhosis and COVID-19. *J Hepatol*. 2020;73(5):1063-1071. doi:10.1016/j.jhep.2020.06.001

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Blood tests	
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		1.3 (1.1–1.7)	0.042
		19 (38)	0.621
		19 (38)	0.025
		(61,000–171,750)	0.197
		11 (22)	0.425
		(4,100–8,370)	0.559
		10/49 (20)	0.387
		11/49 (22)	0.773
		995 (638–1,380)	0.067
		37/48 (77)	0.342
		48 (35–87)	0.176
	(35)	32/48 (67)	0.002
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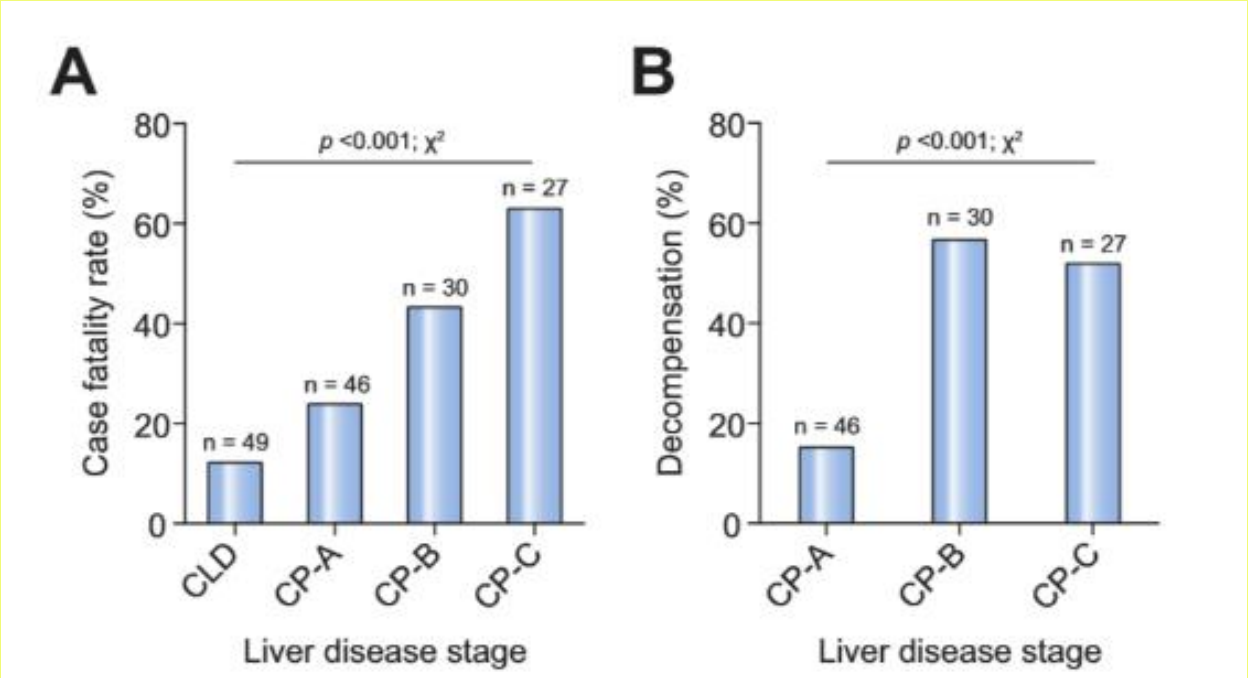
Mortality of COVID19 in cirrhotics 34-39%

Mortality in newly decompensated patients 63%

High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: Preliminary results from an international registry Moon, Andrew M. et al.
Journal of Hepatology, Volume 73, Issue 3, 705 - 708
Iavarone M, D'Ambrosio R, Soria A, et al. High rates of 30-day mortality in patients with cirrhosis and COVID-19. *J Hepatol*. 2020;73(5):1063-1071. doi:10.1016/j.jhep.2020.06.001

COVID and Cirrhosis



High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: Preliminary results from an international registry
Moon, Andrew M. et al.
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COVID and CIrrhosis

What is recommended (AASLD 09.11.2020)

- Test patients with newly decompensated cirrhosis for COVID 19
- Consider primary prophylaxis with beta-blocker therapy instead of screening endoscopy in patients with clinically significant portal hypertension or high risk of decompensation.
- Limit patient exposure

COVID and Viral Hepatitis

What is recommended (AASLD 09.11.2020)

- Continue treatment for hepatitis B and hepatitis C.
- No contraindication to initiating treatment of hepatitis B and C in patients *without* COVID-19.
- Initiating treatment of hepatitis B in a patient *with* COVID-19 is not contraindicated.
- Initiating treatment of hepatitis C in a patient *with* COVID-19 is not routinely warranted and can be deferred until recovered from COVID-19.

COVID and HCC

- Being transplanted for HCC or having cancer at the moment of the COVID-19 diagnosis, was associated with a poor outcome.

What is recommended (AASLD 09.11.2020)

- Arbitrary delay of screening 2 months
- Proceed with liver cancer treatments or surgical resection when able rather than delaying them because of the pandemic.

Becchetti C, Zambelli MF, Pasulo L, et al. Gut 2020;**69**:1832–1840.

COVID and Autoimmune Hepatitis

What is recommended (AASLD 09.11.2020)

- In patients *without* COVID-19: No anticipatory adjustments.
- In patients with AIH on immunosuppression *with* COVID-19: Consider lowering immunosuppression, particularly anti-metabolite dosages (e.g., azathioprine or mycophenolate).

Stable outpatient: Viral hepatitis and PBC, PSC

- There is no evidence that patients with stable chronic liver disease without advanced fibrosis/cirrhosis attributable to hepatitis B and/or C, or cholestatic syndromes such as primary biliary cholangitis or primary sclerosing cholangitis have increased susceptibility to SARS-CoV-2 infection.

COVID and MAFLD

- The impact of nonalcoholic fatty liver disease (NAFLD) on COVID-19 is controversial but metabolic risk factors such **as obesity, diabetes mellitus, and hypertension** are associated with COVID-19 severity.

EASL

All patients with chronic liver disease should adhere to common rules of physical distancing

Patients with chronic liver disease (including compensated cirrhosis)

- Visits to specialized centres can be postponed
- Routine laboratory testing can be performed locally/off-site
- Use telemedicine/visits by phone wherever possible

Specific considerations for

Patients with viral hepatitis:
- No increased risk of a severe course of COVID-19
- Send follow-up prescriptions for patients on antiviral therapy by mail

Patients with NAFLD or NASH:
- May suffer from diabetes, hypertension and obesity, putting them at increased risk of a severe course of COVID-19

Patients with autoimmune liver disease:
- We currently advise against reducing immunosuppressive therapy. Reduction should only be considered under special circumstances after consultation with a specialist
- Emphasis on the importance of vaccination for *Streptococcus pneumoniae* and influenza

Patients with compensated cirrhosis:
- Consider delaying hepatocellular carcinoma) surveillance and screening for varices. Individualized and non-invasive risk assessment should be applied for stratification (see also section on "*Liver-related diagnostic procedures*")

Patients with decompensated liver disease (including hepatocelullar carcinoma)

- Care should be maintained according to guidelines
- Minimal exposure to medical staff, by using telemedicine/visits by phone wherever possible/required to avoid admission
- Listing for transplantation should be restricted to patients with poor short-term prognosis, as transplantation activities/organ donations will likely be reduced in many countries and areas
- Reducing the in-hospital liver transplant evaluation program to the strictly necessary is recommended to shorten hospital stays
- Emphasis on the importance of vaccination for *Streptococcus pneumoniae* and influenza
- Guidelines on prophylaxis of spontaneous bacterial peritonitis and hepatic encephalopathy should be closely followed to avoid admission
- Include testing for SARS-CoV-2 in patients with acute decompensation or acute-on-chronic liver failure

Specific considerations for

Patients actively listed for transplantation:
- SARS-CoV-2 routine testing should be performed before transplantation in both donors and recipients, acknowledging that negative testing cannot completely rule out infection.
- Consent for diagnostic and therapeutic procedures related to transplantation should include the potential risk for nosocomial COVID-19
- Living-donor transplantations should be considered on a case-by-case basis.

Patients with hepatocellular carcinoma

- Care should be maintained according to guidelines, including continuing systemic treatments and evaluation for liver transplantation
- Minimal exposure to medical staff, by using telemedicine/visits by phone wherever possible/required to avoid admission
- In case of COVID-19, early admission is recommended. See also section on "*Inpatient care*"

Patients after liver transplantation

- Maintain care according to guidelines
- Minimal exposure to medical staff, by using telemedicine/visits by phone wherever possible/required to avoid admission
- Emphasis on the importance of vaccination for *Streptococcus pneumoniae* and influenza
- In stable patients, perform local lab testing (including drug levels)
- We currently advise against reducing immunosuppressive therapy. Reduction should only be considered under special circumstances after consultation with a specialist

Post- OLT	Cirrhosis	Viral hepatitis	HCC	Autoimmune hepatitis
Mortality in COVID not augmented	Mortality and risk of decompensation high in cirrhotic COVID patients	No adverse outcomes reported	Possibly worse outcomes in HCC patients with COVID	
NO anticipatory adaptation	Test for COVID in decompensated cirrhosis	Treat HBV and HCV in COVID neg. Patients	Continue treatment if possible	NO anticipatory adaptation
Consider reducing MMF in COVID pos. patients	No adverse outcomes of anticoagulation in COVID pos. patients	Withhold HCV treatment in COVID pos. patients		Consider reducing treatment in COVID pos. patients

General measures in clinical practice

- Limiting outpatient visits to only patients who **must** be seen in person when COVID-19 is prevalent in the community, per local guidance.
- Continue to prioritize new adult patietns with urgent issues and clinically significant liver disease (e.g., jaundice, elevated ALT or AST >500 U/L, recent onset of hepatic decompensation, selected patients with liver cancer, and selected patients for liver transplant evaluation).
- Limit the number of family members/friends who accompany patients to their visits.
- Continue to use phone visits or telemedicine as appropriate and available to replace in-person visits
- Screen all patients for symptoms of COVID-19 or recent exposure (i.e., fever, cough, shortness of breath, sore throat, diarrhea, myalgias, new loss of sense of taste or smell contact with known COVID-19 patients, history of recent domestic or international travel) before entry into the clinical space (e.g., phone call 24 hours prior to scheduled visit), and again at registration or as they enter the clinic.
- Check each patient's temperature and ask about symptoms when they arrive to the clinic or registration desk. o Patients with fever (>38 °C) or symptoms should be referred to the hospital's protocol for symptomatic patients.
- • Consider evaluating patients with COVID-19 symptoms or known exposure in an outpatient clinic or a site dedicated for this purpose. PPE should be

Resources

- AASLD: https://www.aasld.org/about-aasld/covid-19-and-liver
- Uptodate: https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-issues-related-to-liver-disease-in-adults?search=covid%2019%20liver&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=

Papers

- Fix OK, Hameed B, Fontana RJ, et al. Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement. Hepatology. 2020;72(1):287-304. doi:10.1002/hep.31281
- Colmenero J, Rodríguez-Perálvarez M, Salcedo M, et al. Epidemiological pattern, incidence and outcomes of COVID-19 in liver transplant patients [published online ahead of print, 2020 Aug 1]. *J Hepatol*. 2020;S0168-8278(20)30521-3. doi:10.1016/j.jhep.2020.07.040
- Becchetti C, Zambelli MF, Pasulo L, et al. COVID in an international European liver transplant recipient cohortGut 2020;**69**:1832–1840.
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- Singh S, Khan A. Clinical Characteristics and Outcomes of Coronavirus Disease 2019 Among Patients With Preexisting Liver Disease in the United States: A Multicenter Research Network Study. Gastroenterology. 2020;159(2):768-771.e3. doi:10.1053/j.gastro.2020.04.064

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Thank you for your attention: Open for discussion

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