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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Wong GL-H, Wong VW-S, Thompson A, et al. Management of patients with liver derangement during the COVID-19 pandemic: an Asia-Pacific position statement. *Lancet Gastroenterol Hepatol* 2020; published online June 22. https://doi.org/10.1016/S2468-1253(20)30190-4.

Supplementary Table 1. Grading of evidence and recommendations (adapted from the GRADE system).

Quality/Certainly of Evidence	Description
A	High quality evidence from meta-analysis or randomized controlled trials without major limitations; or in the case of non-interventional studies, evidence from high quality observational studies. Further research is unlikely to change our confidence in the estimate of effect.
B	Moderate quality evidence from meta-analysis or randomized controlled trials with obvious limitations or observational studies. Further research is likely to have an important impact on our confidence in the estimate of effect.
C	Low or very low quality evidence from randomized controlled trials or observational studies with major limitations; case series and case reports. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain.
Strength of Recommendation	Description
1	Strong recommendation based on the quality of evidence, presumed patient-important outcomes, and costs.
2	Weaker recommendation because of variability in preferences and values, uncertainty, and higher cost or resource consumption.

Supplementary Table 2. Voting of the recommendation statements.

No.	Statement	Before voting		After voting	
		Grading of evidence	**Grading of recommendations**	**Grading of evidence**	**Grading of recommendations**
Scenario 1	**Should off-label pharmacological treatment for COVID-19 be continued in the case of liver derangement?**				
1A	Patients with COVID-19 and persistent liver derangement should have standard investigations for liver diseases; the choice of investigations would depend on the clinical presentation and pattern of liver injury but should involve at least serological tests for viral hepatitis	C	2	C	1
1B	Patients with abnormal liver function should be closely monitored when using off-label lopinavir–ritonavir, chloroquine, hydroxychloroquine, and tocilizumab, preferably monitored in the setting of clinical trials	C	2	C	1
1C	Off-label treatment for COVID-19 should be withheld in the case of moderate to severe (ie, category 2–3) liver injury	C	1	C	1
Scenario 2	**Should all COVID-19 patients have liver function panel checked routinely?**				
2A	Clinicians should test liver function in hospitalised patients with COVID-19	A	1	C	1
2B	The optimal interval for liver tests is uncertain; however, it would be reasonable to monitor liver tests twice weekly in patients on potentially hepatotoxic medication, patients with pre-existent liver disease, and more frequently in any patients with abnormal liver function	C	2	C	2
Scenario 3	**Should all COVID-19 patients be routinely screened for common chronic liver diseases based on the local prevalence?**				
3A	Patients with COVID-19 and liver derangement should have investigations for the underlying cause, including screening for common liver diseases (eg, viral hepatitis); there is no evidence to support routine screening for chronic liver diseases in patients with normal liver tests	B	1	B	1
3B	Screening for other causes of liver disease might wait until abnormal liver function persists beyond recovery of COVID-19	C	2	C	2
Scenario 4	**Should COVID-19 patients with chronic hepatitis B virus (HBV) infection have antiviral therapy for HBV started when liver derangement develops? What are the risk of drug-drug interaction of medications for chronic liver diseases and the pharmacological treatment for COVID-19?**				

4A	If systemic corticosteroids or other potent immunosuppressants (eg, tocilizumab) are used as COVID-19 therapy for 7 days or longer, screening for HBsAg is recommended; antiviral therapy for HBV should be initiated to avoid HBV reactivation and hepatitis flare in patients with known HBV infection	B	1	B	1
4B	Antiviral therapy for HBV newly diagnosed at the time of presentation with COVID-19 should be started according to the existing international guidelines	A	1	A	1
4C	Concomitant use of tenofovir disoproxil fumarate or tenofovir alafenamide with lopinavir–ritonavir is relatively contraindicated as drug concentration of tenofovir might be increased; tenofovir might be temporarily switched to entecavir during the use of lopinavir–ritonavir in the absence of entecavir resistance	B	1	B	1
4D	Do not stop oral nucleoside antiviral therapy for HBV at the time of COVID-19 to avoid the risk of HBV reactivation and clinical flare.	A	1	B	1
Scenario 5	**What is the potential drug-drug interactions between direct-acting antiviral (DAA) therapy for chronic hepatitis C virus (HCV) infection and pharmacological treatment for COVID-19?**				
5A	Concomitant use of protease inhibitor-containing DAA regimens for hepatitis C virus with lopinavir–ritonavir is contraindicated	A	1	A	1
5B	DAAs should be continued if being taken at the time of COVID-19 diagnosis, unless drug–drug interactions would be problematic or patients are in critical condition	B	1	B	1
5C	If clinically significant drug–drug interactions with COVID-19 therapies are present, DAAs should be deferred until after COVID-19	A	1	A	1
5D	Drug–drug interactions between some new COVID-19 therapies and DAAs should be closely monitored as data are scarce	B	1	C	1
Scenario 6	**What are the precautions and treatments recommended for NAFLD patients?**				
6A	Have heightened awareness of adverse clinical outcomes in patients with NAFLD who have COVID-19, especially if they have diabetes	C	1	C	1
6B	Blood pressure and glycaemic control should be monitored and managed in patients with NAFLD who have COVID-19	C	2	C	2
Scenario 7	**How should hepatocellular carcinoma (HCC) surveillance be performed during the COVID-19 pandemic?**				
7A	Prioritise resources to continue usual surveillance imaging (with or without tumour markers) in patients who need hepatocellular carcinoma surveillance the most (eg, patients with cirrhosis or high hepatocellular carcinoma risk scores)	A	1	B	1
7B	An arbitrary delay of 3 months in patients with relatively low risk of hepatocellular carcinoma is reasonable and might be necessary if COVID-19 outbreaks are ongoing in the region	C	1	C	2

Scenario 8	**How to manage HCC patients during the COVID-19 pandemic?**				
8A	Patients with hepatocellular carcinoma who have COVID-19 should have their hepatocellular carcinoma treatment deferred until after recovery from COVID-19	C	2	C	2
8B	Bridging transarterial chemoembolisation, radiofrequency ablation, or systemic chemotherapy might be considered in selected patients with hepatocellular carcinoma who have COVID-19 when surgical resection is deferred	C	2	C	2
Scenario 9	**How should variceal screening be performed during the COVID-19 pandemic?**				
9A	Postponement of elective upper gastrointestinal endoscopic examination for variceal screening in patients with no history of gastrointestinal bleeding until a COVID-19 outbreak is under control is reasonable and might be necessary if COVID-19 outbreaks are ongoing in the region	C	1	C	1
9B	Non-invasive tools (eg, Baveno VI criteria, platelet-to-liver stiffness measurement ratio, liver and spleen stiffness measurement) might be used to identify patients who are at high risk of having clinically significant varices	B	1	B	1
9C	Endoscopic eradication of oesophageal varices should be done following a variceal bleed	A	1	A	1
9D	In the case that emergency or urgent upper endoscopy is warranted in suspected or confirmed cases of COVID-19, it should be done under a negative-pressure room when available with strict isolation precautions, and all endoscopy personnel should wear appropriate personal protective equipment, including N95 respirator and waterproof protective gown	B	1	B	1
Scenario 10	**What are the special arrangements and precautions in patients needing liver transplantation during the COVID-19 pandemic?**				
10A	Reduce the number of patients coming to transplantation clinic per session for assessment; only assess patients with hepatocellular carcinoma or patients with high MELD scores who are likely to benefit from immediate liver transplantation listing	C	1	C	1
10B	Telehealth should be available to most transplantation centres	C	1	C	2
10C	Clear instruction to patients awaiting liver transplantation to maintain physical distancing and to not travel during the COVID-19 pandemic	B	1	B	1
10D	All potential donors (cadaveric and live donors) and recipients should be tested for SARS-CoV-2 RNA and transplantation will only proceed with negative donors to negative recipients	B	1	B	1
Scenario 11	**What are the special arrangements and precautions in managing post-transplantation patients during the COVID-19 pandemic?**				
11A	Check for any drug–drug interactions if COVID-19 therapies are needed in patients after transplantation	A	1	A	1
11B	It is not necessary to reduce immunosuppression or stop mycophenolate for asymptomatic patients after transplantation	B	1	B	1

11C	Patients or their caregivers with COVID-19 symptoms should not visit the liver transplantation clinic	C	1	B	1
11D	All patients after transplantation should avoid an unnecessary outpatient visit; an arbitrary delay of 3 months is reasonable and might be necessary if COVID-19 outbreaks are ongoing in the region	C	2	B	1
11E	Emphasise well known prevention measures to patient after transplantation: frequent hand washing, cleaning frequently touched surfaces, staying away from large crowds, staying away from individuals who are ill, etc.	C	1	B	1
Scenario 12	**Should patients with decompensated cirrhosis be sent to Intensive Care Unit (ICU) if they develop respiratory failure due to COVID-19?**				
12A	In patients with known decompensated cirrhosis, decisions about intensive care unit support should be made on a case-by-case basis, taking into account baseline liver function, previous episodes of liver decompensation, and transplant eligibility	C	2	C	2
12B	Spontaneous bacterial peritonitis in patients with COVID-19 and decompensated cirrhosis should be treated with broad spectrum antibiotics with no drug–drug interactions with the COVID-19 therapies	C	2	C	2

Supplementary Table 3. International Drug-Induced Liver Injury Expert Working Group classification of the severity of drug-induced liver injury.[28]

Category	Severity	Description
1	Mild	ALT ≥5 or ALP ≥2 and total bilirubin <2 x ULN
2	Moderate	ALT ≥5 or ALP ≥2 and total bilirubin ≥2 x ULN, or symptomatic hepatitis
3	Severe	ALT ≥5 or ALP ≥2 and total bilirubin ≥2 x ULN, or symptomatic hepatitis and 1 of the following criteria: - INR ≥1.5 - Ascites and/or encephalopathy, disease duration <26 weeks, and absence of underlying cirrhosis - Other organ failure due to drug-induced liver injury
4	Fatal/transplantation	

ALP, alkaline phosphatase; ALT, alanine aminotransferase; INR, international normalized ratio; ULN, upper limit of normal

Supplementary Table 4. Deranged liver tests among patients with COVID-19.

Author	N	Patients with pre-existing liver diseases	Patients with deranged liver tests
Guan *et al.* [30]	1099	2·3%	22% abnormal AST, 21% abnormal ALT
Huang *et al.* [31]	41	2·0%	31%
Chen *et al.* [9]	99	Not reported	43%
Shi *et al.* [32]	81	0·6%	53%
Xu *et al.* [33]	62	11%	16%
Yang *et al.* [34]	52	Not reported	29%
Fan *et al.* [29]	148	Not reported	37%

ALT, alanine aminotransferase; AST, aspartate aminotransferase.