

The Liver's Fate Amid COVID-19 Pandemic

Muhammad Begawan Bestari¹, Siti Aminah Abdurachman¹

1 Division of Gastroenterohepatology, Department of Internal Medicine, Hasan Sadikin General Hospital-Faculty of Medicine University of Padjadjaran, Bandung, Indonesia.

Conflict-of-interest statement: The authors declare that there is no conflict of interest regarding the publication of this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Muhammad Begawan Bestari, MD, MHS, PhD, FASGE, Division of Gastroenterology, Department of Internal Medicine, Hasan Sadikin General Hospital-Faculty of Medicine, University of Padjadjaran, Jl. Pasteur No.38, Bandung, Jawa Barat, Indonesia 40161.

Email: begawanb@yahoo.com

Telephone: +62(022) 2034953/55

Fax: +62(022) 2032216

ORCID ID: 0000-0002-6911-8213

Received: November 8, 2020

Revised: November 21, 2020

Accepted: November 23, 2020

Published online: December 21, 2020

ABSTRACT

Corona-virus disease (COVID-19) affected medical services worldwide because of its pandemic nature; including patients with chronic liver disease (CLD). Generally, there are three situations in which CLD patients can be affected by the coronavirus. Patients who have pre-existing liver conditions, especially those that need constant follow-up, will be exposed during follow-up visits to the hospital and are more vulnerable to infection. Second, patients with COVID-19 who have liver function derangements and incidental findings of ongoing CLD, especially those with cirrhosis will have more severe courses of the disease and possible acute-on-chronic liver failure. Finally, patients who undergo treatment for CLD who

are infected with COVID-19, where drug-drug interactions are possible (e.g. lopinavir-ritonavir) that may increase the concentration of the protease inhibitor DAA for Hepatitis C treatment. This review aims to provide guidelines for managing patients with CLD amid the pandemic, and how we move forward after the lockdown.

Key words: Chronic liver disease; Hepatitis B; Hepatitis C; Cirrhosis; COVID-19

© 2020 The Authors. Published by ACT Publishing Group Ltd. All rights reserved.

Bestari MB, Abdurachman SA. The Liver's Fate Amid COVID-19 Pandemic. *Journal of Gastroenterology and Hepatology Research* 2020; 9(6): 3367-3372 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/3026>

INTRODUCTION

In December 2019, a cluster of patients were diagnosed with pneumonia of unknown origin in Wuhan, China^[1]. The cause was then identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a zoonotic virus that can be transmitted from humans to humans, now called corona-virus disease 2019 (COVID-19). As of 1 November 2020, the virus has infected more than 46 million people, and there were 1.2 million deaths worldwide^[2]. Social distancing and hygiene controls have been implemented in some areas; however one major concern is hospital-associated transmission to healthcare providers and patients^[3]. Furthermore asymptomatic patients also have the potential to spread the disease, resulting most non-urgent hospital visits risky. As the population falls victim to the virus, healthcare system and providers has developed methods to limit transmission using telemedicine and other unique methods^[4]. Nevertheless, for patients who previously needed to be followed up at the hospital regularly, such as those with chronic liver disease (CLD), there may be long lasting impacts in the future due to missed follow up, and patients reluctance to come back to the hospital for their check-up even after the lockdown period is over.

CHRONIC LIVER DISEASE AND COVID-19

The relationship between CLD and COVID-19 is not yet fully understood yet. To date, there is no evidence that stable CLD has increased susceptibility to COVID-19. In a recent meta-analysis, the reported

prevalence of CLD among COVID-19 patients at baseline was 3%, with the main cause of viral hepatitis, either hepatitis B virus (HBV) or hepatitis C virus (HCV)^[5]. Similarly, Xu, et al. reported that the prevalence of pre-existing liver diseases among COVID-19 patients was around 2-10%^[6]. A pooled analysis from six studies (four comparing severe vs. non-severe cases and two comparing survival) reported that CLD was not associated with increased odds of more severe COVID-19 infection (OR 0.96) or mortality (OR 2.33)^[7]. This might suggest that patients with stable CLD are not at higher risk of contracting COVID-19; however it is noteworthy that the risk of infection or more severe disease course may differ according to the nature of the CLD. The Asian Pacific Association for the Study of the Liver (APASL) Expert consensus stated that patients with stable chronic HBV, HCV, non-alcoholic fatty liver (NAFLD)/metabolic associated fatty liver disease (MAFLD), or cholestatic liver disease may have increased risk of COVID-19 infection^[8].

Viral hepatitis

A recent study of 105 patients showed that liver injury in chronic HBV and COVID-19 co-infection were more likely to have a more severe course of illness and worse prognosis including higher mortality and complications^[9]. A similar study by Chen, et al. of 123 patients, 15 among whom had HBV co-infection and COVID-19, also found that co-infected patients had a higher severity rate compared to patients with COVID-19 patients alone (46.7% vs. 24.1%, respectively). Furthermore, the mortality rate was also worse with HBV co-infection (13.3% HBV co-infection vs. 2.8% without HBV co-infection)^[10], suggesting that patient with HBV co-infection may be more prone to liver injury. It is important to note that these studies involve only a limited number of patients only. Currently, no studies have reported the effect of HCV on COVID-19 infection, and the reported incidence was as low as < 0.1% (3/5700)^[11].

MAFLD

From a retrospective cohort involving 202 patients, it was reported that MAFLD was associated with higher risk of COVID-19 disease progression (6.6% vs. 44.7% $p < 0.0001$) and longer viral shedding time (17.5 ± 5.2 days vs. 12.1 ± 4.4 days $p < 0.0001$) compared to patients without MAFLD^[12]. This result is consistent even in younger patients with MAFLD (< 60 years)^[13]. The reason behind it may be attributed to adipose tissue that can act as reservoir for the virus in aggravating the inflammatory response^[14].

Cirrhosis

Cirrhotic patients are in an immunocompromised state that renders them more susceptible to various infections due to cirrhosis-associated immune dysfunction. COVID-19 patients with pre-existing cirrhosis have an increased mortality rate, especially for Child-Pugh class C^[15,16]. An initial report from China found that patients with high MELD scores survived, while those with lower MELD scores did not and more patients with Child-Pugh class C died, while those with Child-Pugh class B did not^[16]. This may suggest that clinical decompensation may have more value in predicting the outcome of COVID-19 in patients with cirrhosis. Interestingly, in a prospective multicenter study, reported that there was no significant difference in the rates of mortality or transfer to hospice care in patients with cirrhosis and COVID-19 compared to those with cirrhosis alone (30% vs. 20%); similarly, there was no significant difference in the presence of acute-on-chronic liver failure (ACLF) (29.7% vs. 22.8%)^[17]. Therefore, due to the small sample size and mixed results it is currently difficult to conclude the impact of cirrhosis on the disease progression of coronavirus.

APPROACH TO NON-COVID-19 CLD PATIENT

To decrease the potential spread of the disease via hospital-associated transmission, patient's visits should be limited or at least staggered to prevent crowding and to achieve proper social distancing at the clinics. Several professional associations including the APASL^[8,18], American Association for the Study of the Liver Diseases (AASLD)^[19], and the European Association for the Study of the Liver (EASL)^[20] released position statements and consensus. For patients with viral hepatitis undergoing ongoing treatment, it is recommended to continue treatment whenever possible. Reducing the patient visit to the hospital using telemedicine and sending follow-up medication via mail, may be beneficial in reducing the risk of contracting COVID-19. However, for patients with poor compliance direct observation may be necessary. Education regarding social distancing should be emphasized, it is important that patients with CLD realize that they may have increased susceptibility (Figure 1). Similarly, patients with MAFLD should also be made aware of their condition and susceptibility, because obesity alone is a risk factor for more severe COVID-19 infection^[21,22]. Lifestyle modification, weight loss, and diabetes glycemic control should be emphasized^[18,20], and patients should be informed of their crucial role in managing MAFLD.

Patients with cirrhosis are at higher risk of more severe infections and higher mortality as the degree of decompensation increased; therefore, they are vulnerable to delayed standard care during the pandemic. To reduce admissions, guidelines to prevent spontaneous bacterial peritonitis, gastrointestinal hemorrhage, and hepatic encephalopathy should be enforced and prophylaxis should be given accordingly. In patients with low risk of hepatocellular carcinoma (HCC) an arbitrary monitoring delay of 2-3 months is deemed acceptable when the region is experiencing an outbreak^[18,19]. Patients with elevated alpha fetoprotein levels should be prioritized. The arbitrary delay should be evaluated closely; such a delay may have long lasting impact on the quality of cirrhosis care as described by Tapper and colleague^[23]. The longer the delay in monitoring, the more backlog cases that healthcare providers have to deal with, this may overwhelm the capacity.

Several international societies have advocated non-urgent gastrointestinal procedures such as endoscopy to be deferred during the pandemic due to risk transmission via respiratory and gastric secretions^[24,25]. Nevertheless, variceal bleeding is a potentially fatal complication in patients with cirrhosis, similar to HCC screening there should be balance of risk and benefit in performing screening endoscopy. The use of non-invasive assessment such as the Baveno VI criteria^[26] and liver stiffness measurement with transient elastography have a good predictive value to identify clinically significant varices^[27]. Following variceal bleeding endoscopic eradication of esophageal varices should be performed. Patients with emergency gastrointestinal bleeding should be scheduled for emergency endoscopy regardless of COVID-19 status, provided appropriate infection control equipment is available (Figure 2)^[18].

APPROACH TO COVID-19 PATIENTS WITH NEWLY DIAGNOSED LIVER DISEASE

It is not uncommon to have liver function test derangements during the course of COVID-19 infection, some studies reported the incidence to be as high as 16-53%^[18,28-31]. The cause of increased liver function can be attributed to COVID-19 itself, drug related

effects, sepsis, and underlying liver disease. It remains unknown as to what extent COVID-19 directly causes elevated liver function tests or is a secondary phenomenon from the physiological response to the infection. ACE2 receptor which SARS-CoV-2 use as an entry point, is found in abundance in cholangiocytes, and the expression of ACE2 is comparable to that of alveolar type 2 cells^[32,33]. By contrast, the ACE2 expression in hepatocytes is twentyfold less compared to cholangiocytes^[32]. This finding may suggest that liver abnormalities may not be caused by hepatocyte damage, but rather cholangiocyte dysfunction and other causes such as drug related causes or systemic physiologic responses.

It is recommended by the APASL working group of liver derangement that, during COVID-19 pandemic, one should perform standard investigations when levels of alanine aminotransferase (ALT) and aspartate transaminase (AST) or both are elevated^[18]. Routine testing for HBV is recommended, especially in endemic areas, whereas HCV screening is recommended for individuals with histories of transfusions, injection of illicit drugs use, and organ transplantation before the advent of donor screening. Similarly, AASLD also recommended considering etiologies other than COVID-19, including hepatitis A, B, and C^[19]. In patients with HBV infection there is no contraindication to initiate treatment, especially when the patient fulfills the treatment criteria recommended by international guidelines (HBV DNA > 2000 IU/mL, ALT more than upper limit of normal (ULN), or ALT 2x ULN)^[34,35] the initiation of treatment would be justified. However, for patients who did not fulfill the treatment criteria, the initiation of antiviral therapy should be discussed with the patient due to the long-term duration of the

treatment. For patients with hepatitis C, it is recommended to defer treatment until COVID-19 infection is resolved^[19,20].

It is difficult to establish drug-induced liver injury; because the derangement of liver function test is common among COVID-19 patients. The use of off-label pharmacological treatment should be evaluated carefully, and it is necessary to monitor liver tests. It is possible to stop the drug when there are signs of liver injury such as ALT > 5 times ULN, alkaline phosphatase (ALP) > 2 times ULN, total bilirubin > 2 ULN, the presence of coagulopathy, and liver decompensation^[18]. If the treatment given is part of a clinical trial, the management of liver derangement should follow the study protocol.

The transport of patients with COVID-19 should be limited as it increases personal contact with the patients and the risk of transmission; therefore, imaging such as ultrasound, MRI/MRCP, is not recommended unless it is highly likely to alter management. Ultrasound indicated for surveillance should be deferred until recovery^[20].

APPROACH TO PATIENT WITH CLD INFECTED WITH COVID-19

In patients with chronic HBV who are infected with COVID-19, it is recommended to continuing treatment^[18,20]. Justification for the recommendation is due to the fact that some drugs such as corticosteroids and tocilizumab, which used to treat COVID-19, may cause reactivation of HBV and hepatitis flare^[36-38]. The results of preliminary report from the RECOVERY trial stated that dexamethasone reduced death in mechanically ventilated patients by

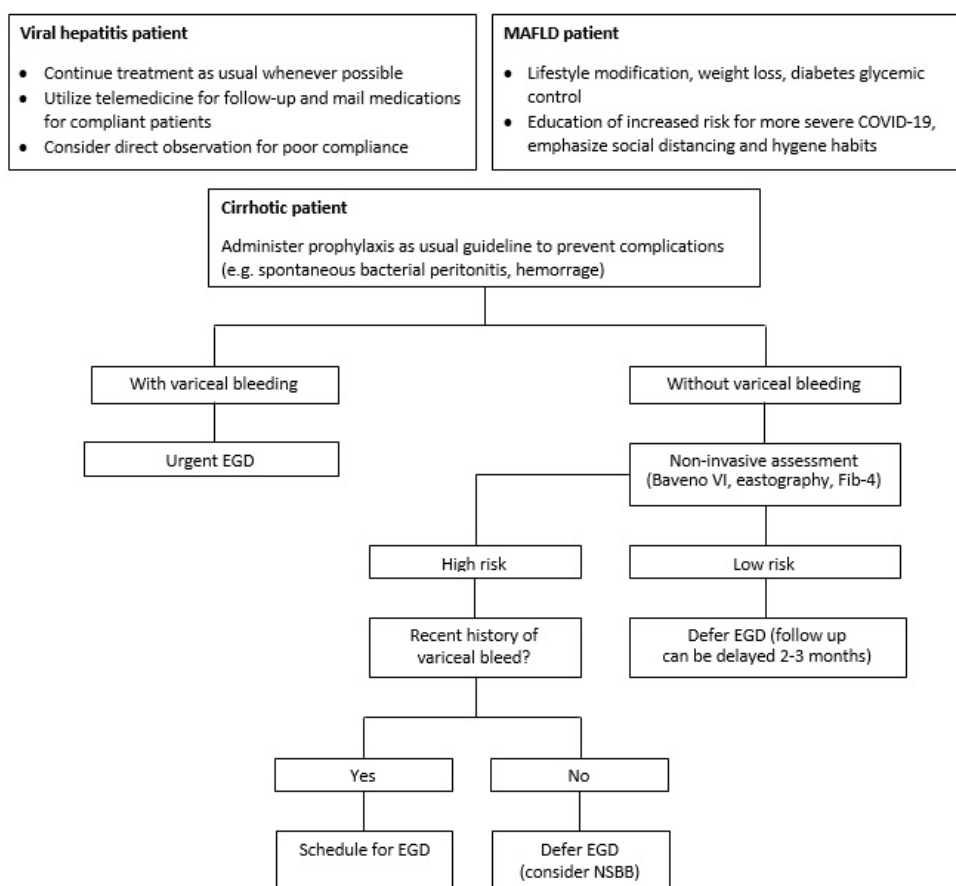


Figure 1 Proposed algorithm for patients with chronic liver disease during and after the pandemic, based on current consensus. EGD: esophagogastroduodenoscopy; FIB-4: fibrosis-4 scoring; NSBB: non-selective beta blocker.

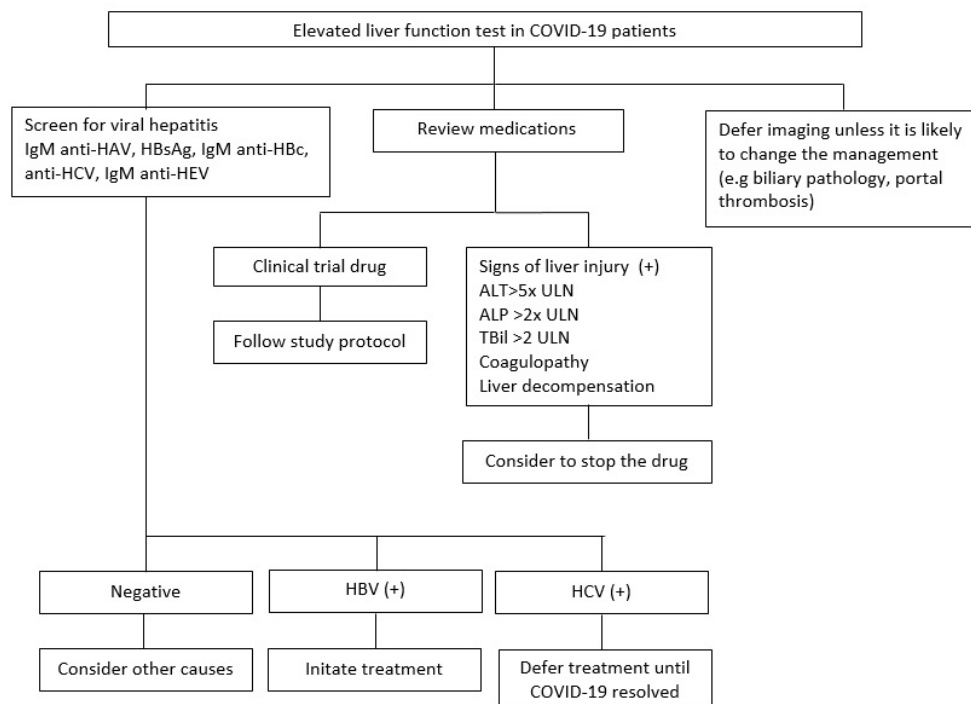


Figure 2 Proposed algorithm for patient with elevated liver function test in patients with COVID-19. ALT: alanine aminotransferase; ALP: alkaline phosphatase; TBil: total bilirubin; ULN: upper limit of normal.

one-third; in patients with oxygen support, death was reduced by one-fifth and no benefit was shown for patients without oxygen support.^[39] Similarly, tocilizumab a monoclonal antibody for interleukin-6 has been shown to be an effective treatment for COVID-19 patients with cytokine storm risk^[40]; however, it has been reported that tocilizumab might reactivate HBV and cause fulminant hepatic failure^[38].

For patients with hepatitis C it is recommended to continue treatment with direct acting antiviral (DAA) as most of the COVID-19 treatment has no drug-drug interaction^[18-20]. However, protease inhibitor DAA regimen should not be continued with lopinavir-ritonavir as it might increase the drug concentration of the protease inhibitor DAA. Premature termination of DAA therapy may decrease the success rate from 100% to 74%^[41]. Patients with MAFLD and those with cirrhosis infected with COVID-19 are particularly at risk for clinical deterioration; therefore, early admission is advised. In patients with known decompensated liver cirrhosis, decisions to transfer care to an intensive unit should be made on a case-by-case basis.

CONCLUSION

COVID-19 is a new disease; there are plenty of aspects of the virus that we do not understand as of now yet, including its relationship to and impact on the liver. A lot of data is needed to further understand the impact of the virus to the liver as liver derangements are quite common. Research into novel drugs against COVID-19 should be evaluated for drug-drug interactions and liver toxicities, and clinical trials of new drugs should also incorporate regular hepatic monitoring. Because the current consensus guidelines will potentially change as we understand more about the disease, physicians should be updated regularly on any advances made. Finally, this review is aimed as a guide during the pandemic to prevent patients with from becoming infected by SARS-CoV-2, to follow-up patients during the pandemic to reduce backlog of cases, and to manage patients with CLD and COVID-19.

ACKNOWLEDGMENTS

This study was supported by Internal Research Grant from University of Padjadjaran.

REFERENCE

- Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med.* 2020; **382**: 727-33. [DOI: 10.1056/NEJMoa2001017]; [PMCID: PMC7092803]
- World Health Organization (WHO). Coronavirus disease (COVID-19) Weekly Epidemiological Update, 1 November 2020. Available at: <https://www.who.int/publications/m/item/weekly-epidemiological-update---3-november-2020> Accessed: 4 November 2020.
- Lee IK, Wang CC, Lin MC, Kung CT, Lan KC, Lee CT. Effective strategies to prevent coronavirus disease-2019 (COVID-19) outbreak in hospital. *J Hosp Infect.* 2020; **105**: 102-3. [DOI: 10.1016/j.jhin.2020.02.022]; [PMCID: PMC7124248]; [PMID: 32142886]
- Yetmar ZA, Issa M, Munawar S, Burton C, Pureza V, Sohail MR, Mehmood T. Inpatient Care of Patients with COVID-19: A Guide for Hospitalists. *Am J Med.* 2020; Apr 25. [DOI: 10.1016/j.amjmed.2020.03.041]; [PMCID: PMC7182745]; [PMID: 32339477]
- Mantovani A, Beatrice G, Dalbeni A. Coronavirus disease 2019 and prevalence of chronic liver disease: A meta-analysis. *Liver Int.* 2020; **40**: 1316-20. [DOI: <https://doi.org/10.1111/liv.14465>]; [PMID: 32329563]
- Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int.* 2020; **40**: 998-1004. [DOI: 10.1111/liv.14435]; [PMID: 32170806]; [PMCID: PMC7228361]
- Lippi G, de-Oliveira MHS, Henry BM. Chronic liver disease is not associated with severity or mortality in Coronavirus disease 2019 (COVID-19): a pooled analysis. *Eur J Gastroenterol Hepatol.*

- 2020; Apr 10. [DOI: 10.1097/MEG.0000000000001742]; [PMID: 32282549]
8. APASL Covid-19 Task Force; Lau G, Sharma M. Clinical practice guidance for hepatology and liver transplant providers during the COVID-19 pandemic: APASL expert panel consensus recommendations. *Hepatol Int.* 2020; **14**: 415-28. [DOI: 10.1007/s12072-020-10054-w]; [PMID: 32447721]; [PMCID: PMC7245190]
 9. Zou X, Fang M, Li S, Wu L, Gao B, Gao H, Ran X, Bian Y, Li R, Yu S, Ling J, Li D, Tian D, Huang J. Characteristics of Liver Function in Patients With SARS-CoV-2 and Chronic HBV Coinfection. *Clin Gastroenterol Hepatol.* 2020; **S1542-3565**: 30821-1. [DOI: 10.1016/j.cgh.2020.06.017]; [PMID: 32553907]; [PMCID: PMC7294291]
 10. Chen X, Jiang Q, Ma Z, Ling J, Hu W, Cao Q, Mo P, Yang R, Gao S, Gui X, Xiong Y, Li J, Zhang Y. Clinical Characteristics of Hospitalized Patients with SARS-CoV-2 and Hepatitis B virus Coinfection. *medRxiv.* 2020. [DOI: 10.1101/2020.03.23.20040733]
 11. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA.* 2020; **323**: 2052-5059. [DOI: 10.1001/jama.2020.6775]; [PMCID: PMC7177629]; [PMID: 32320003]
 12. Ji D, Qin E, Xu J, Zhang D, Cheng G, Wang Y, Lau G. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. *J Hepatol.* 2020; **73**: 451-3. [DOI: 10.1016/j.jhep.2020.03.044]; [PMID: 32278005]; [PMCID: PMC7141624]
 13. Zhou Y-J, Zheng KI, Wang X-B, Yan H-D, Sun Q-F, Pan K-H, Wang T-Y, Ma H-L, Y-P.Chen, J.George, Zheng M-H. Younger patients with MAFLD are at increased risk of severe COVID-19 illness: A multicenter preliminary analysis. *J Hepatol.* 2020; **73**: 719-21. [DOI: 10.1016/j.jhep.2020.04.027]
 14. Ryan PM, Caplice NM. Is Adipose Tissue a Reservoir for Viral Spread, Immune Activation, and Cytokine Amplification in Coronavirus Disease 2019? *Obesity.* 2020; **28**: 1191-4. [DOI: 10.1002/oby.22843]; [PMID: 32314868]; [PMCID: PMC7264526]
 15. Qi X, Liu Y, Wang J, Fallowfield J, Wang J, Li X, Shi J, Pan H, Zou S, Zhang H, Chen Z, Li F, Luo Y, Mei M, Liu H, Wang Z, Li J, Yang H, Xiang H, Li X, Liu T, Zheng M-H, Liu C, Huang Y, Xu D, Li X, Kang N, He Q, Gu Y, Zhang G, Shao C, Liu D, Zhang L, Li X, Kawada N, Jiang Z, Wang F, Xiong B, Takehara T, Rockey DC. for the COVID-Cirrhosis-CHESS Group. Clinical course and risk factors for mortality of COVID-19 patients with pre-existing cirrhosis: a multicentre cohort study. *Gut.* 2020. [DOI: 10.1136/gutjnl-2020-321666]; [PMID: 32434831]
 16. Qi X, Wang J, Li X, Wang Z, Liu Y, Yang H, Li X, Shi J, Xiang H, Liu T, Kawada N, Maruyama H, Jiang Z, Wang F, Takehara T, Rockey DC, Sarin SK. for the COVID-Cirrhosis-CHESS Group. Clinical course of COVID-19 in patients with pre-existing decompensated cirrhosis: initial report from China. *Hepatol Int* 2020. [DOI: 10.1007/s12072-020-10051-z]; [PMCID: PMC7242176]; [PMID: 32440857]
 17. Bajaj JS, Garcia-Tsao G, Biggins S, Kamath PS, Wong F, McGeorge S, Shaw J, Pearson M, Chew M, Fagan A, Rodriguez RdIR, Worthington J, Olofson A, Weir V, Trisolini C, Dwyer S, Reddy KR. Comparison of mortality risk in patients with cirrhosis and COVID-19 compared with patients with cirrhosis alone and COVID-19 alone: multicentre matched cohort. *Gut.* 2020. [DOI: 10.1136/gutjnl-2020-322118]; [PMCID: PMC7371484]; [PMID: 32660964]
 18. Wong GL-H, Wong VW-S, Thompson A, Jia J, Hou J, Lesmana CRA, Susilo A, Tanaka Y, Chan W-K, Gane E, Ong-Go AK, Lim S-G, Ahn SH, Yu M-L, Piratvisuth T, Chan HL-Y. on behalf of the Asia-Pacific Working Group for Liver Derangement during the COVID-19 Pandemic. Management of patients with liver derangement during the COVID-19 pandemic: an Asia-Pacific position statement. *Lancet Gastroenterol Hepatol.* 2020; **5**: 776-87. [DOI: 10.1016/S2468-1253(20)30190-4]; [PMID: 32585136]; [PMCID: PMC7308747]
 19. Fix OK, Hameed B, Fontana RJ, Kwok RM, McGuire BM, Mulligan DC, Pratt DS, Russo MW, Schilsky ML, Verna EC, R.Loomba, Cohen DE, Bezerra JA, Reddy KR, Chung RT. AASLD. Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement. Released June 25, 2020. *Hepatology.* 2020. [DOI: 10.1002/hep.31281]; [PMCID: PMC7262242]; [PMID: 32298473]
 20. 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 Rep.* 2020. [DOI: 10.1016/j.jhepr.2020.100169]; [PMID: 32835190]; [PMCID: PMC7402276]
 21. Cai Q, F.Chen, Wang T, Luo F, Liu X, Wu Q, He Q, Wang Z, Liu Y, Liu L, Chen J, Xu L. Obesity and COVID-19 Severity in a Designated Hospital in Shenzhen, China. *Diabetes Care.* 2020; **42**: 1392-8. [DOI: 10.2337/dc20-0576]; [PMID: 32409502]
 22. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, Holden KA, Read JM, Dondelinger F, Carson G, Merson L, Lee J, Plotkin D, Sigfrid L, Halpin S, Jackson C, Gamble C, Horby PW, Nguyen-Van-Tam JS, Ho A, Russell CD, Dunning J, Openshaw PJM, Baillie JK, Semple MG. on behalf of the ISARIC4C investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ.* 2020. [DOI: 10.1136/bmj.m1985]; [PMID: 32444460]; [PMCID: PMC7243036]
 23. Tapper EB, Asrani SK. The COVID-19 pandemic will have a long-lasting impact on the quality of cirrhosis care. *J Hepatol.* 2020; **73**: 441-5. [DOI: 10.1016/j.jhep.2020.04.005]; [PMID: 32298769]; [PMCID: PMC7194911]
 24. Gralnek IM, Hassan C, Beilenhoff U, Antonelli G, Ebigbo A, Pellisé M, Arvanitakis M, Bhandari P, Bisschops R, Hooft JEV, Kaminski MF, Triantafyllou K, Webster G, Pohl H, Dunkley I, Fehrke B, Gazic M, Gjergje T, Maasen S, Waagenes W, de Pater M, Ponchon T, Siersema PD, Messmann H, Dinis-Ribeiro M. ESGE and ESGENA Position Statement on gastrointestinal endoscopy and the COVID-19 pandemic. *Endoscopy.* 2020; **52**: 483-90. [DOI: 10.1055/a-1155-6229]; [PMID: 32303090]; [PMCID: PMC7295280]
 25. American Society for Gastrointestinal Endoscopy (ASGE). Gastroenterology Professional Society Guidance on Endoscopic Procedures During the COVID-19 Pandemic. Available at: <https://www.asge.org/home/advanced-education-training/covid-19-asge-updates-for-members/gastroenterology-professional-society-guidance-on-endoscopic-procedures-during-the-covid-19-pandemic>. Accessed: 20 July 2020.
 26. Franchis RD. Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol.* 2015; **63**: 743-52. [DOI: 10.1016/j.jhep.2015.05.022]; [PMID: 26047908]
 27. Wong GLH, Kwok R, Hui AJ, Tse Y-K, Ho K-T, Lo AOS, Lam KLY, Chan HCH, Lui RA, Au KHD, Chan HLY, Wong VWS. A new screening strategy for varices by liver and spleen stiffness measurement (LSSM) in cirrhotic patients: A randomized trial. *Liver Int.* 2018; **38**: 636-44. [DOI: 10.1111/liv.13560]; [PMID: 28853196]
 28. Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, Zhang Y, Huang

- S, Liu Z, Cheng J. Clinical Features of COVID-19-Related Liver Functional Abnormality. *Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association*. 2020; **18**: 1561-6. [DOI: 10.1016/j.cgh.2020.04.002]; [PMID: 32283325]; [PMCID: PMC7194865]
29. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020; **395**: 507-13. [DOI: 10.1016/S0140-6736(20)30211-7]; [PMID: 32007143]; [PMCID: PMC7135076]
 30. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020; **395**: 497-506. [DOI: 10.1016/S0140-6736(20)30183-5]; [PMID: 31986264]; [PMCID: PMC7159299]
 31. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *The Lancet Respiratory medicine*. 2020; **8**: 475-81. [DOI: 10.1016/S2213-2600(20)30079-5.7102538]; [PMID: 32105632]; [PMCID: PMC7102538]
 32. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A, Zhou J, Shi G, Fang N, Fan J, Cai J, Fan J, Lan F. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. *bioRxiv*. 2020. [DOI: 10.1101/2020.02.03.931766]
 33. Kumar P, Sharma M, Kulkarni A, Rao PN. Pathogenesis of Liver Injury in Coronavirus Disease 2019. *J Clin Exp Hepatol* 2020. [DOI: 10.1016/j.jceh.2020.05.006]; [PMID: 32837092]; [PMCID: PMC7237376]
 34. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *Journal of hepatology*. 2017; **67**: 370-98. [DOI: 10.1016/j.jhep.2017.03.021]; [PMID: 28427875]
 35. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, Chen HL, Chen PJ, Chien RN, Dokmeci AK, Gane E, Hou JL, Jafri W, Jia J, Kim JH, Lai CL, Lee HC, Lim SG, Liu CJ, Locarnini S, Al Mahtab M, Mohamed R, Omata M, Park J, Piratvisuth T, Sharma BC, Sollano J, Wang FS, Wei L, Yuen MF, Zheng SS, Kao JH. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatology international*. 2016; **10**: 1-98. [DOI: 10.1007/s12072-015-9675-4]; [PMID: 26563120]; [PMCID: PMC4722087]
 36. He Q, Song X, Huang Y, Huang W, Ye B, Luo H, Luo H, Wu L, Wang Z, Chen W, Zhang L. Dexamethasone Stimulates Hepatitis B Virus (HBV) Replication Through Autophagy. *Medical science monitor: international medical journal of experimental and clinical research*. 2018; **24**: 4617-24. [DOI: 10.12659/MSM.906250]; [PMID: 29972684]; [PMCID: PMC6064191]
 37. Alzghari SK, Acuna VS. Supportive Treatment with Tocilizumab for COVID-19: A Systematic Review. *J Clin Virol*. 2020; **127**: 104380. [DOI: 10.1016/j.jcv.2020.104380]; [PMID: 32353761]; [PMCID: PMC7194791]
 38. Sonneveld MJ, Murad SD, van der Eijk AA, de Man RA. Fulminant Liver Failure due to Hepatitis B Reactivation During Treatment With Tocilizumab. *ACG Case Rep J*. 2019; **6**: e00243. [DOI: 10.14309/crj.000000000000243]; [PMID: 32042838]; [PMCID: PMC6946203]
 39. Horby P, Lim WS, Emberson J, Mafham M, Bell J, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, T. Felton, Chadwick D, Rege K, Fegan C, Chappell LC, Faust WN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. RECOVERY Collaborative Group. Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report. *N Engl J Med*. 2020 Jul 17; NEJMoa2021436. [DOI: 10.1056/NEJMoa2021436]; [PMID: 32678530]; [PMCID: PMC7383595]
 40. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. *J Med Virol*. 2020; **92**: 814-8. [DOI: 10.1002/jmv.25801]; [PMID: 32253759]; [PMCID: PMC7262125]
 41. Marshall MC, Herrera JL. Lack of Patient Compliance in Real-World Practice Negatively Affects Sustained Viral Response Rates to Direct Acting Agent Therapy for Hepatitis C. *Dig Dis Sci*. 2018; **63**: 3228-32. [DOI: 10.1007/s10620-018-5247-5]; [PMID: 30128645]