Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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References

1. Singh S, Khan A. Gastroenterology 2020;159:768–771.
2. Felsenstein S, et al. Clin Immunol 2020;215:108448.
3. Albillos A, et al. J Hepatol 2014;61:1385–1396.
4. Ji D, et al. J Hepatol 2020;73:451–453.
5. D'Amico G, et al. Aliment Pharmacol Ther 2014;39:1180–1193.
6. SECURE cirrhosis and EASL COVID-Hep Registry. Combined weekly update – 12 May 2020. Available at: https://covid-hep.net/updates.html. Accessed May 12, 2020.
7. Zhou YJ, Zheng KI, Wang XB, et al. J Hepatol 2020;73:719–721.
8. Zheng Z, Peng F, Xu B, et al. J Infect 2020;81:e16–e85.

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Acute-on-Chronic Liver Failure: Possibly the Main Culprit of Increased Mortality in COVID-19 Patients with Liver Disease

Dear Editors:

We read with great interest the article "Clinical Characteristics and Outcomes of COVID-19 Among Patients with Pre-Existing Liver Disease in the United States: A Multi-Center Research Network Study" by Singh et al.[1] The study is one of the first to describe the impact of coronavirus disease 2019 (COVID-19) in patients with preexisting liver disease. The mechanism of increased mortality in this population is not well defined and is possibly multifactorial. We want to report a case to highlight that one of the possible explanations of higher mortality is the development of acute-on-chronic liver failure (ACLF) in liver disease patients with COVID-19.

A 38-year-old man with cryptogenic liver cirrhosis (Child B9, Model for End-stage Liver Disease score of 20) and history of variceal bleeding and on the national transplant list presented with a 3-day history of fever and dry cough. He was febrile but otherwise stable vitally. Clinically, he was jaundiced with stigmata of chronic liver disease. His initial labs showed pancytopenia, an international normalized ratio of 1.9, bilirubin of 3.74 mg/dL, albumin of 2.4 g/dL, alkaline phosphatase of 335 IU/L, alanine aminotransferase of 40 IU/L, and aspartate aminotransferase of 64 IU/L. A chest radiograph on admission revealed bilateral infiltrates. A nasopharyngeal and throat swab was positive for COVID-19 polymerase chain reaction.

During the hospitalization, he developed grade II encephalopathy and was started on lactulose. On day 3 of the hospitalization, owing to progressive respiratory failure, the patient was intubated and mechanical ventilation was initiated. During his intensive care unit stay, he received broad-spectrum antibiotics and convalescent plasma of a recovered COVID patient. The patient developed ACLF with a bilirubin reaching 56.4 mg/dL and an international normalized ratio of 3.5. He developed refractory metabolic acidosis requiring continuous renal replacement therapy. His European Association for the study of Liver - Chronic Liver Failure organ failure score was 17, ACLF grade 3 with 5 organs involved. Unfortunately, on day 14 of hospitalization patient expired because of multiorgan failure.

ACLF is a syndrome characterized by acute hepatic decompensation (the development of ascites, encephalopathy, gastrointestinal hemorrhage, and/or bacterial infections), organ failure (liver, kidney, brain, coagulation, respiration, and circulation) as defined by the Chronic Liver Failure organ failure score, and 28-day mortality exceeding 15%, resulting from different types of insults to the liver.[2,3] The prevalence of ACLF ranges from 24% to 40% of patients with liver cirrhosis who are hospitalized. ACLF may develop in patients with previously compensated or decompensated cirrhosis, and in patients with the underlying chronic liver disease without cirrhosis.[3] Hepatitis B and alcohol are the most common underlying etiologies of chronic liver disease in patients with ACLF[4]; however, nonalcoholic fatty liver disease–related liver disease is expected to take the lead in coming years.[3] Bacterial infections, active alcoholism, and exacerbation of hepatitis B are the most common triggers of ACLF, but in 20%–45% of cases, the trigger remains unknown.[3,5]

The hallmark of ACLF is excessive systemic inflammation, and patients with ACLF have higher levels of inflammatory markers and proinflammatory cytokines—IL-6, IL-1β, and IL-8. The inducers of systemic inflammation can be exogenous or endogenous and viruses have been described previously to trigger inflammation.[3] Immunopathology resulting from uncontrolled activation of the immune system and excessive production of proinflammatory cytokines has been proposed as a mechanism of tissue injury in ACLF, as these patients have a higher degree of systemic inflammation and the degree of inflammatory markers is linearly associated with the number of organ failures.[2] In patients with COVID-19, a cytokine storm has been reported characterized by increased IL-2, IL-7, granulocyte-colony stimulating factor, and tumor necrosis factor-α.[6] We believe the excessive inflammatory response associated with COVID-19 can serve as a trigger of ACLF in patients with underlying chronic liver disease and potentially explains the

increased mortality in patients with liver disease observed in the study. Previously, it has been reported that cirrhotic patients who develop influenza have a high risk of severe disease, organ failure, and death.[7] In addition to excessive systemic inflammation, other mechanisms may also contribute to the development of ACLF. Direct tissue damaged caused by infectious agents and failed tolerance to inflammatory response at the tissue level can also contribute to the ongoing tissue damage.[2,3]

It would be interesting to know the incidence of acute on chronic liver disease in patients with preexisting liver disease who had mortality in the study by Singh et al.[1] Further research is warranted to elucidate the mechanisms of increased mortality in patients with liver disease who develops COVID-19. Furthermore, physicians should be alerted to the possibility of the development of ACLF in this population.

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References

1. Singh S, et al. Gastroenterology 2020;159:768771.
2. Arroyo V, et al. J Hepatol 2015;62(1 Suppl):S131–S143.
3. Hernaez R, et al. Gut 2017;66:541–553.
4. Abbas Z, et al. Hepatol Int 2015;9:366–372.
5. Moreau R, et al. Gastroenterology 2013;144:1426–1437; 1437.e1–9.
6. Mehta P, et al. Lancet 2020;395:1033–1034.
7. Schütte A, et al. J Hepatol 2019;70:797–799.

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Reply. We thank Khan et al,[1] Verma et al,[2] and Romana et al,[3] for their interest in our study and for highlighting several important strengths and limitations of the findings described in our study. Ours was the first study evaluating the impact of preexisting liver disease on coronavirus disease 2019 (COVID-19). We compared the outcomes of patients with preexisting liver disease and without liver disease in a cohort of patients with COVID-19 in the United States. We found that patients with preexisting liver disease were at increased risk for poor outcomes compared to patients without liver disease, and the risk was markedly higher in patients with cirrhosis.

In the letter to the editor, Khan et al[1] report a case highlighting the development of acute-on-chronic liver failure (ACLF) in liver disease patients with COVID-19. Khan et al suggest that one of the possible explanations of higher mortality in patients with preexisting liver diseases could be related to the development of ACLF. Our study could not determine the possible reasons for poor outcomes of COVID-19 in patients with preexisting liver disease, and we hypothesized these are likely multifactorial, and further studies are needed. We also did not specifically study the incidence of ACLF in our cohort of patients with preexisting disease. However, patients with severe COVID-19 can develop multiorgan failure that can eventually result in mortality. We agree with Khan et al[1] that the development of ACLF in liver disease patients with COVID-19 can potentially result in increased mortality and needs further extensive studies.

Most of the points highlighted by Verma et al[2] in their letter to the editor are related to the inherent limitations of the database or the small sample size of patients available early in the pandemic. They have correctly identified that subgroup analysis based on etiology of liver diseases, including nonalcoholic fatty liver disease, was not performed. We performed our analysis on a relatively small cohort of patients with preexisting liver disease available at the time of study early in the pandemic. However, we did a subgroup analysis of patients with cirrhosis and highlighted the higher risk of mortality and hospitalization in this vulnerable group of patients. We agree with Verma et al[2] that the lower lymphocyte count among patients with preexisting liver disease can be explained by the pancytopenia observed in patients with cirrhosis. The database currently does not allow regression analysis to adjust for confounding factors. However, we performed a propensity score matching analysis, an equally accepted method to adjust for the cofounders. Propensity matching was performed using a greedy nearest-neighbor matching algorithm with a caliper of 0.1 pooled standard deviations.

We appreciate the work done by Romana et al[3] in examining the correlation between liver chemistry abnormalities and IL-6 serum levels in patients with COVID-19, highlighting the role of liver injury and inflammatory state or cytokine storm during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In our study, we reported elevations in liver chemistry test results from baseline values, suggesting possible liver injury from SARS-CoV-2. However, we did not study the possible reasons for the elevations in liver chemistries. We agree with Romana et al that one of the possible causes for liver function tests abnormalities can be related to cytopathic viral effect and patients with chronic liver disease could be severely affected by the cytokine storm. However, other causes should be considered, and further larger prospective studies are needed.

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