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.

analysis synthesizing data from the Minnesota trial and European trials reported that "gFOBT screening made little or no difference on CRC incidence compared with no-screening, neither annually nor biennially."[7]

The referral rate to colonoscopy after gFOBT testing was substantially greater in the Minnesota trial (28% and 38% in biennial and annual screening arms, respectively)[8] than in the European trials (~5%).[4–6] This is likely because in the Minnesota trial, most gFOBTs were rehydrated, which resulted in higher positivity rates.[8] It is reasonable to assume that the high colonoscopy referral rate in the Minnesota trial drove the association between gFOBT screening and lower CRC incidence. We acknowledge that gFOBT screening is a 2-step process and the gFOBT is "meant to risk-stratify individuals that would benefit from a colonoscopy";[1] however, in the context of CRC incidence reduction, this would mean risk-stratifying individuals according to likelihood of harboring premalignant polyps and existing data do not indicate that the gFOBT can perform such a function.[9]

There is hope for fecal immunochemical test (FIT)-based screening to have a greater impact on CRC incidence. As Shaukat et al[1] note, Levin et al[10] reported reductions in CRC incidence following implementation of a FIT-based screening program in a community-based population; however, this study was observational and more robust data are needed from randomized controlled trials of programmatic application of FIT screening at different FIT positivity thresholds.

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Conflicts of interest
The authors disclose no conflicts.

Most current article
https://doi.org/10.1016/j.cgh.2021.05.061

Liver Injury in Severe COVID-19 Disease: Need a Closer Look!

Dear Editor:

We read with great interest the study by Chew et al[1] concluding that liver test abnormalities associated with COVID-19 per se do not lead to liver insufficiency or death. Whereas, COVID-19-related ischemic, hypercoagulable, and hyperinflammatory disease states are significant predictors of death. Some of the issues need further consideration.

First, mortality in COVID-19 is determined by disease severity at hospital admission and standards of intensive care unit support. Ischemia, hyperinflammation, and hypercoagulability are hallmarks of severe COVID-19 disease. Previous studies have shown correlation of significant liver injury with severity of COVID-19.[2,3] Moreover, these patients often require use of potentially hepatotoxic drugs, such as tocilizumab, which might contribute to liver injury. Significant liver injury more often suggests severe COVID-19 disease and all these factors are likely correlated. The acute liver injury in the presence of COVID-19 is multifactorial and in the absence of liver biopsy, it is often difficult to determine the actual cause.

Second, in patients with significant liver injury, mortality is also determined by the presence and severity of preexisting liver disease. In the current study, $<5\%$ of patients had liver cirrhosis. Patients with liver cirrhosis present unique challenges. Immune dysfunction in cirrhosis led to increased susceptibility to infection and aberrant inflammatory response during infection, collectively known as cirrhosis-associated immune dysfunction.[4] The current therapeutic armamentarium to treat severe COVID-19 in patients with severe liver disease is limited. Most of the specific drugs for moderate to severe COVID-19 disease including remdesivir, lopinavir–ritonavir, tocilizumab, and high-dose dexamethasone are contraindicated in the presence of severe liver disease. Moreover, the data on clinical outcomes for these difficult-to-treat patients are limited. In the SECURE-Cirrhosis and COVID-Hep registries, hepatic decompensation events and mortality were more frequent with increasing severity of liver disease.[5] Severe COVID-19 might also precipitate acute-on-chronic liver failure.

Third, in the current study, the diagnosis of ischemic liver injury was considered only after 2 days of vasopressor support. At this stage, it is often too late and patients have very high mortality.

In summary, the clinical relevance of this important study on liver injury and COVID-19 disease could have been enhanced by accounting for the previously mentioned factors.

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Conflicts of interest
The authors disclose no conflicts.

Most current article
https://doi.org/10.1016/j.cgh.2021.05.030

Reply. We thank Dr Jindal for comments regarding our article on liver injury and COVID-19. Herein we provide a response to the 3 points raised.

First, we entirely agree with Dr Jindal's assessment of our study. We show that severe liver injury reflects severity of COVID-19 vis-à-vis therapeutic strategies aimed at treating the disease (COVID drugs) and/or at keeping the patient alive (eg, vasopressors). Notably, severe liver injury only occurred in a minority of patients (3%). In the absence of liver biopsy (which would not have been justified) that would confirm ischemic or drug-induced injury, we had to rely on associations and temporal relationships as is often done clinically. Autopsy studies of patients who died from COVID-19 have shown histopathologic changes in the liver consistent with disturbed intrahepatic circulation[1] and upregulation of proteins involved in fibrosis, necrosis, fatty acid oxidation, and other markers of immune activation, with very little viral replication.[2] Unfortunately, these studies lack a clinical-pathologic correlation.

Second, we could not find an association between mortality by COVID-19 and the presence of preexisting liver disease. In our study, which included consecutive patients admitted with COVID-19, only 38 (4.5%) had chronic liver disease without cirrhosis and 13 (1.5%) had cirrhosis. This is very similar to rates reported in another large cohort from an academic center with only 31 (1.4%) patients with cirrhosis.[3] As pointed out in that study, the lack of association between chronic liver disease/cirrhosis and mortality could be caused by these low numbers. Additionally, and as mentioned by Dr Jindal, international registries that include large numbers of patients with cirrhosis have reported worse outcomes mostly in patients with decompensated cirrhosis.[4] Only 3 patients in our cohort had decompensated cirrhosis. Interestingly, in a careful analysis of patients with cirrhosis admitted during the initial stages of the COVID-19 pandemic, mortality in patients admitted for complications of cirrhosis (without COVID-19) was not significantly different from that of age- and gender-matched patients with cirrhosis admitted with COVID-19 but was significantly higher than that of patients admitted with COVID-19 (without cirrhosis).[5]

Third, in our definition of ischemic liver injury, we required that a patient be on vasopressors for at least 2 days. We defined the ischemic state as 2 consecutive days on vasopressors to avoid capturing patients who may have required transient vasopressor use peri-intubation. We agree that patients who received vasopressors are more severely ill and have a higher mortality. The multivariate analysis in Table 3 of our study has the objective of identifying different predictors of death with the main objective of examining whether significant liver injury was an independent predictor of death. It was not.

The comments by Dr Jindal highlight our 2 main conclusions, that significant liver injury in patients hospitalized with COVID-19 mainly results from concomitant processes/drugs during hospitalization; and that this significant liver injury does not result in liver insufficiency and is not an independent predictor of death.

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Conflicts of interest
The authors disclose no conflicts.

Most current article
https://doi.org/10.1016/j.cgh.2021.05.064

Network Meta-analysis of Ulcerative Colitis Pharmacotherapies: Carryover Effects From Induction and Bias of the Results

Dear Editor:

In their network meta-analyses (NMAs) of treatments for ulcerative colitis (UC), Singh et al[1] did not take into