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Impact of Pre-existing Chronic Liver Disease on the Outcome of Patients with COVID-19 Disease

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We read the article by Singh et al. [1] with great interest that demonstrated the presence of chronic liver disease (CLD) as a risk factor for hospitalization and mortality among COVID-19 patients. This study is a timely report and provokes many national and international health agencies to incorporate presence of CLD as a high-risk criterion in the policy decisions and treatment algorithms for the management of COVID-19. The greatest strength of this study was derivation of results from a multi-centric large database. However, certain issues in the study merit a close attention.

Firstly, SARS-CoV2 infection has an intricate pathophysiology related to immune-depletion of B/T/NK cells and a hyperactive cytokine response, which has been linked to immune escape phenomenon and macrophage activation. [2] Patients with CLD often represent varying stages of immune dysfunction ranging from functional failure, mitochondrial stress to complete anergy of adaptive and innate immune cells.[3] Singh et al. [1] reported a lower lymphocyte count among patients with CLD as compared with controls (1.9 vs. 2.5/mcL), which could represent greater immune-suppression in COVID-19 patients with underlying CLD than controls. Some postulation earlier have suggested higher M-1 to M-2 macrophage transition in patients with cirrhosis and COVID-19 rendering poor clearance of virus and higher cytokine response. [4] However, more research is needed to explore the association between immune defects in cirrhosis and COVID-19 disease.

Secondly, the term “CLD” constitute a spectrum of patients with varying prognosis ranging from chronic hepatitis, cirrhosis, decompensated cirrhosis to acute-on-chronic liver failure. [5] The “SECURE cirrhosis” and “EASL COVID-Hep registry” have recently come up with weekly updates on CLD patients and COVID-19. [6] They have reported higher mortality in patients with COVID-19 with underlying cirrhosis (36%) as compared with absence of cirrhosis (7%). Hence, the authors must explore the outcomes in COVID-19 patients with underlying CLD

with regard to cirrhosis or no-cirrhosis and stratify results according to the stages of cirrhosis.

Thirdly, majority of patients (42%) in the study by Singh et al. [1] had fatty liver disease or nonalcoholic steatohepatitis (NASH) as the underlying CLD in the liver disease group. Patients with non-alcoholic fatty liver disease (NAFLD) were recently shown to have progressive course, higher hepatic dysfunction and prolonged viral shedding among COVID-19 patients.[4] But the diagnosis of NAFLD in some patients in that study was made by hepatic steatosis index which may have its own fallacies in making the diagnosis of hepatic steatosis in a setting of other causes of raised transaminases as in COVID-19 disease. [4] Moreover, separate effect of underlying nonalcoholic fatty liver (NAFL) or NASH on the outcome was not available in that study. [4] Since, Singh et al. [1] in their database had definite information regarding underlying fatty liver and NASH, it would be interesting to know the effect of these two separate phenotypes on the outcome in COVID-19 patients. Recent data has also suggested the effect of age on the impact of metabolic-dysfunction-associated fatty liver disease (MAFLD) on the poor outcome in patients with COVID-19; younger patients having poorer outcome. [7] Hence it would be worthwhile exploring this aspect as well from the data provided by Singh et al.[1]

Fourthly, despite propensity score matching, the COVID-19 patients with underlying CLD had higher chronic respiratory and chronic kidney disease as compared with controls (p=0.01). On the contrary, D-Dimer levels were higher in controls (2.9 vs. 1.0 mcg/mL). Chronic respiratory or renal diseases and D-Dimer levels were recently shown as independent risk factors for mortality in COVID-19. [8] Therefore, to balance all confounders, the authors must perform a multivariable logistic-regression or Cox-regression to identify if CLD or cirrhosis or

any etiology of CLD was an independent predictor of mortality or poor outcome among COVID-19 patients.

Lastly, there was some missing data for laboratory values among patients with CLD and statistical test of significance between laboratory values of cases and controls was not done.

As mentioned correctly in the manuscript, the findings were generalizable only to the patients having a contact with health care organization. The post hoc statistical power of comparisons was acceptable at 95% confidence interval and 80% power. Therefore, this study has led to a stepping stone for future studies that will explore the presence of CLD as a disease-modifier among COVID-19 patients.

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