

Cholestatic liver injury in COVID-19 is a rare and distinct entity and is associated with increased mortality

Dear Editor,

Current evidence indicates that the development of acute hepatocellular liver injury during coronavirus disease 2019 (COVID-19) is associated with more severe COVID-19 disease [1]. Since SARS-CoV2 is able to enter the liver via the ACE2 receptor proteins located on the epithelium of bile ducts, direct viral cholangiocyte injury is theoretically a possible pathogenic mechanism of the virus resulting in cholestatic liver injury [2]. Supporting this idea, a recent meta-analysis reporting serum alkaline phosphatase (ALP) elevations occurring in up to 13.7% of patients [3], a case series describing the clinical/histologic features in three patients with COVID-19 cholangiopathy [4] and a recent study reporting higher fatality rates in COVID-19 patients with cholestasis [5].

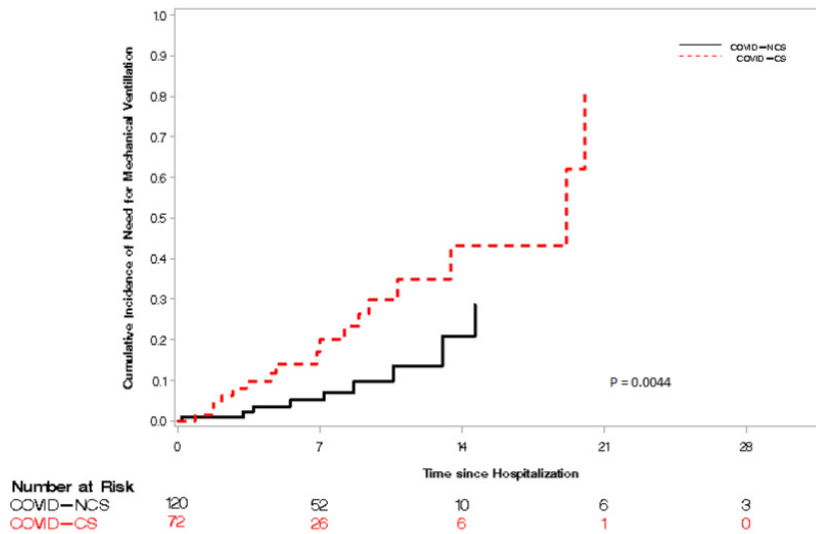
We conducted a retrospective, observational study that included consecutive adult patients in 12 hospitals within the Northwell Health System from 1 March 2020 to 27 April 2020 during the first wave of the COVID-19 pandemic in New York to explore the prevalence and outcomes of cholestatic liver injury in COVID-19 [6] (Methods S1). Patients were considered to have COVID-19 cholestasis (COVID-CS) if on admission, the serum ALP level was $>3\times$ ULN. ULN for ALP was defined as 125 U L^{-1} . Patients were followed until up to 28 days after admission, death or discharge. Propensity score matching (PSM) was performed (1:2) to select a control cohort of COVID-19 patients without cholestasis ($\text{ALP} \leq 3\times$ ULN) admitted during the same time period. The primary clinical outcome was mortality, and we explored the association between COVID-CS and need for mechanical ventilation (MV)/mortality using multivariate Cox proportional regression analysis. Kaplan–Meier method was used to analyse the cumulative incidence of in-hospital need for MV and mortality.

During the study period, 10 895 patients were hospitalized of which 72 (0.7%) met the definition of COVID-CS. After PSM, 192 patients were included in this study – 72 patients with COVID-CS and 120 controls. There were no significant

differences in age, gender, race, ethnicity or insurance type between the two cohorts, and comorbidities were evenly matched (Table S1). Patients with COVID-CS usually had higher liver tests but aspartate aminotransferase levels (AST) and alanine aminotransferase (ALT) levels were only marginally higher – 102 U L^{-1} vs 52 U L^{-1} , $P < 0.001$, and 83 U L^{-1} vs 36 U L^{-1} , $P < 0.001$, respectively. 33.3% of COVID-CS patients died compared with 19.2% of controls, $P = 0.027$, and the cumulative incidence of the need for MV and in-hospital mortality was significantly higher in COVID-CS (Table S2 and Figures 1a/b). Amongst the overall cohort ($n = 192$), age, heart failure (HF), chronic kidney disease (CKD), malignancy and COVID-CS – HR 1.79 (1.00–3.19), $P = 0.04$, were associated with a higher likelihood of mortality on univariate analysis. These same variables were also associated with a higher need for MV. After adjusting for age and the presence of HF, malignancy and CKD on Cox regression analysis, COVID-CS continued to be associated with a higher likelihood of MV – aHR 3.99 (1.50–10.62), $P = 0.006$, and mortality – aHR 2.09 (1.12–3.90), $P = 0.02$. Of note, 24 of 72 COVID-CS patients died in-hospital within 28 days and 11 additional COVID-CS patients passed in-hospital after 28 days (censored in the current analysis).

COVID-CS appears to be a distinct entity in COVID-19 and is associated with a higher likelihood of death compared with PSM controls. Our findings suggest that SARS-CoV2 may induce a direct viral toxic effect on the cholangiocytes, likely via the ACE2 receptor, which is resulting in cholestatic liver injury. As such, our findings provide indirect evidence of another possible mechanism for the pathogenesis of liver injury in COVID-19. Moreover, the occurrence of cholestatic liver injury appears to be associated with a higher need for MV in time-dependent analyses. Other mechanisms of liver injury such as cytokine storm, drug-induced liver injury, ischaemia and exacerbation of pre-existing, undiagnosed liver disease could also be contributing to the hepatic laboratory abnormalities seen in our study [7]. Astonishing elevations in AST and ALT have been frequently

(a) Cumulative Incidence of Need for Mechanical Ventilation by Days of Hospitalization



(b) Cumulative Incidence of In-Hospital Mortality

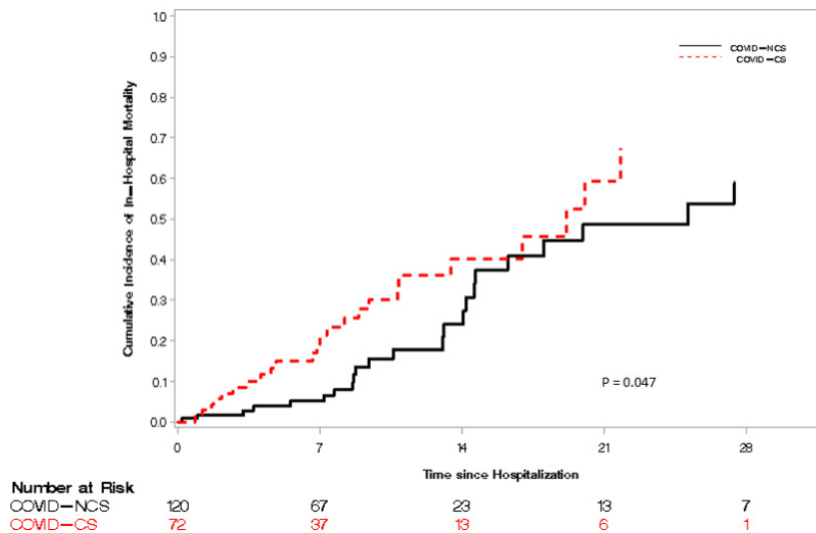


Fig. 1 Kaplan-Meier Survival Curves for COVID-CS vs PSM Control (COVID-NCS) of the Cumulative Incidence of In-Hospital Need for Mechanical Ventilation (a) and Mortality (b). COVID-CS ($ALP > 3x ULN$), control* ($ALP \leq 3x ULN$); $ULN = 125 U L^{-1}$). *PSM COVID-CS cohort (1:2 ratio) for age, gender, race, insurance and comorbidities (CAD, CLD, COPD, DM, ESRD, HF, HTN). CAD, coronary artery disease, CLD, chronic liver disease, COPD, chronic obstructive pulmonary disease, DM, diabetes, ESRD, end-stage renal disease, HF, heart failure, HTN, hypertension, PSM, propensity score matching, ULN, upper limit of normal.


reported in severe COVID-19 – often associated with an extreme hyper-inflammatory response representing a cytokine storm [8]. However, the elevations of AST/ALT in COVID-CS were not impressive. Sepsis-induced cholestasis could also

be contributing to the occurrence of cholestasis. However, the median serum total bilirubin in the COVID-CS cohort was only 0.8 mg dL^{-1} which represents levels much less than what is typically seen in sepsis-induced cholestasis [9].

Our study is limited by its retrospective nature, and thus, we are unable to definitively rule out pre-existing chronic liver disease including co-existing/pre-existing biliary pathology. Our findings raise two important questions. The first is why does cholestatic liver injury occur in only a small subset of COVID-19 patients (less than 1%)? The second question is why is cholestasis in COVID-19 associated with a mortality rate of at least one-third of cases and a twofold increase in mortality compared with evenly matched controls? Future studies, including long-term data of COVID-19 patients with cholestatic liver injury, are needed to determine whether they resolve or develop a chronic cholangiopathic disease.

Conflict of interest

The authors have no relevant conflicts of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Admission clinical and laboratory characteristics after PSM.

Table S2. Outcomes after PSM.

Methods S1. Methods. 