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LETTER TO THE EDITOR

Is positivity for hepatitis C virus antibody predictive of lower risk of death in COVID-19 patients with cirrhosis?

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Abstract

Liver injury has been reported in coronavirus disease 2019 (COVID-19) cases but the impact of pre-existing liver damage and related etiology have not been completely elucidated. Our research interests include the potential reciprocal influence of COVID-19 and pre-existing liver damage related to hepatitis C virus (HCV) infection, in particular. To this end, we have evaluated three cohorts of patients admitted at three Italian hospitals during the coronavirus pandemic; these included 332 patients with COVID-19 and 1527 patients with HCV who were from established real-world antiviral treatment study cohorts (sofosbuvir/velpatasvir), with either liver disease (various severities; n = 1319) or cirrhosis (n = 208). Among the COVID-19 patients, 10 had cirrhosis (3%), including 7 of metabolic origin and 3 of viral origin. Mortality among the COVID-19 patients was 27.1%, with 70% of those with cirrhosis of metabolic etiology having died. Cirrhosis, older age, low white blood cell count and lymphocyte count being identified as risk predictors of death [odds ratio (OR) = 13.7, 95% confidence interval (CI): 2.59-83.01, P = 0.006; OR = 1.05, 95%CI: 1.03-1.08, P = 0.0001; OR = 1.09, 95%CI: 1.36-1.16, P = 0.001; OR = 0.61, 95%CI: 0.39-0.93, P = 0.023, respectively]. In the two cohorts of HCV patients, COVID-19 diagnosis was

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made in 0.07% of those with liver disease and 1% of those with cirrhosis. Thus, the prevalence of HCV antibodies among COVID-19-infected patients was comparable to that currently reported for the general population in Italy. Amongst the COVID-19 patients, pre-existing metabolic cirrhosis appears to be associated with higher mortality, while HCV antibodies may be suggestive of "protection" against COVID-19.

Key Words: Hepatitis C virus; Hepatitis B virus; Cirrhosis; COVID-19; Sofosbuvir; Velpatasvir

Core Tip: This ongoing study aims to investigate the potential reciprocal influence of coronavirus disease 2019 (COVID-19) and pre-existing cirrhosis. To date, it has included 332 patients with COVID-19 admitted to three Italian hospitals during the current pandemic, as well as two large cohorts of hepatitis C virus (HCV) patients from real-world antiviral treatment (pangenotypic sofosbuvir/velpatasvir combination) studies. Despite the limited COVID-19 sample size, cirrhosis was found to be associated with higher mortality, with the majority of deaths related to cirrhosis of metabolic origin. The very low prevalence of COVID-19 in the HCV cohorts supports a possible protective role of HCV antibodies.

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TO THE EDITOR

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome-coronavirus type-2 (SARS-CoV-2) presents a spectrum of clinical manifestations; although, it predominantly results in severe respiratory disease that is associated with significant morbidity and mortality. Early reports of COVID-19 cases described hepatic manifestations, but the pathogenesis of liver injury remains unclear. The role of a pre-existing liver disease related to infections with either the hepatitis B virus (HBV) or hepatitis C virus (HCV) [± human immunodeficiency virus (HIV) co-infection] or to metabolic liver damage with concomitant obesity and diabetes may be relevant. In a large cohort of SARS-CoV-2 patients in the United States, among which 41.7% of cases had comorbid metabolic disease, HBV and HCV infections were determined to play a marginal role, being reported in only 0.1% and < 0.1%, respectively[1]. In SARS-CoV-2 patients from China, however, the rate of HBV infection was 2.1%, reflecting the greater local prevalence of HBV[2]. Otherwise, data on replicative status of these hepatitis patients are lacking. As the global prevalence of HBV and HCV infections is geographically variable[3,4], data from Europe may help improve our understanding of the reciprocal impact of SARS-CoV-2 and HCV/HBV. We have focused our recent research on determining the liver function markers that show abnormalities in routine laboratory testing, including markers of HBV/HCV ± HIV co-infections, and rates of pre-existing cirrhosis in patients hospitalized with COVID-19 in Italy. Simultaneously, we have investigated the prevalence of COVID-19 among two real-world cohorts of HCV patients who achieved cure by sofosbuvir/velpatasvir (SOF/VEL) combination antiviral treatment in over 97% of the cases[5,6].

We prospectively collected demographic, clinical and laboratory data of patients treated at three hospitals in Northern and Southern Italy from March 7 to May 7, 2020. These hospitals represent areas with different COVID-19 prevalence and the patients represent consecutive admissions with SARS-CoV-2 diagnosis.

Simultaneously, we interviewed all the HCV patients enrolled in two original HCV real-world treatment studies on pangenotypic SOF/VEL treatment recently published

by our collaborative group[3,4]. The interviews were conducted with an "ad hoc" questionnaire, and patients were excluded from analysis if they had died before the COVID-19 outbreak. The first study was unrestricted for HCV genotype (GT) or degree of fibrosis (n = 1319 total, 21% with cirrhosis), while the second focused on GT3 infections with compensated cirrhosis and portal hypertension (n = 208). Pre-COVID-19 death excluded 29 (2.1%) of the patients in the pangenotypic study and 8 (3.8%) in the GT3 cirrhosis study. Characteristics of these patients were reported[3,4].

In our subsequent observational prospective study, the prevalence of positivity for HCV antibodies (Abs) and hepatitis B surface antigen (HBsAg) among the COVID-19 patients was compared to the recently reported rates of prevalence of HCVAbs (1.37%) and HBsAg (0.8%-1%) in our country[7,8]. Baseline demographical and clinical characteristics of patients enrolled in our prospective study were reported as mean ± standard deviation or median and range for continuous variables, and as frequency and percentages for categorical variables. Group comparisons were carried out using Wilcoxon rank-sum test for continuous variables and Pearson's chi-square or Fisher's test, as appropriate, for categorical variables.

We prospectively evaluated 332 patients consecutively admitted with COVID-19. The demographic and laboratory results are summarized in Table 1. Mortality rate was 27.1% (Supplementary Table 1). Among the total patients, 91 (27.4%) had increased alanine aminotransferase and 81 (24.3%) had increased aspartate aminotransferase at admission, with death rates of 26.1% and 22.2% among those subgroups, respectively. Moreover, only 4.7% of the total patients showed increased liver enzymes during hospitalization, but 36.0% of those died. In total, 10 patients (3.0%) had pre-existing cirrhosis, of metabolic origin in 7 and of viral origin in 3, the latter including 2 HIV co-infections. Considering the subset of COVID-19 patients with cirrhosis, 70% died (P = 0.005). Among patients with cirrhosis and leucopenia 50% died. Among patients with cirrhosis only one had antiHBc antibodies.

Among the COVID patients, only 10 (3.0%) showed HCVAbs positivity. Only 1 of those 10, however, showed detectable HCV-RNA; the remaining appeared to have spontaneous resolution or treatment-induced HCV-RNA clearance. None of the patients in the group admitted for COVID were under antiviral treatment. Among the HCV-RNA un-reactive COVID patients, 2 had cirrhosis (1 died due to lung cancer, the other was HIV co-infected). Three of the HCVAbs-positive non-cirrhotic patients also died; the first was 97-years-old, the second was 86-years-old with a history of cardiac rhythm abnormalities, and the third was 80-years-old and the single HCV-RNA-reactive case mentioned above. The age distribution of the COVID-19 patients with HCVAbs positivity is presented in Supplementary Table 1. The frequency of HCVAbs among subjects with increased alanine aminotransferase at baseline (6.6%) was significantly higher than in patients with normal liver enzymes (6.6% *vs* 1.8%; P = 0.038). HBsAg positivity occurred in 4 patients (1.2%), all of who were under treatment by nucleotide analogs that resulted in HBV-DNA un-reactive status. The 1 death among this subgroup represented an HIV co-infection with cirrhosis. Discounting the patient who died of lung cancer, 7 out of the 10 cirrhotic patients who died had a non-viral etiology.

Cirrhosis, older age, low counts for white blood cells and lymphocytes were predictors of death [odds ratio (OR) = 13.7, 95% confidence interval (CI): 2.59-83.01, P = 0.006; OR = 1.05, 95%CI: 1.03-1.08, P = 0.0001; OR = 1.09, 95%CI: 1.36-1.16, P = 0.001; OR = 0.61, 95%CI: 0.39-0.93, P = 0.023, respectively].

Among the HCV infection patients from the real-world antiviral treatment cohorts, 1 (0.07%) with cirrhosis in the pangenotypic study and 2 (1%) in the GT3 cirrhosis study reported COVID-19 ascertained infection; all who were between the ages of 45-65, recovered. All the remaining patients showed no symptoms or, in cases of suspected symptoms, had negative COVID-19 molecular testing results.

These results suggest that pre-existing liver cirrhosis of metabolic origin is associated with higher COVID-19-related mortality. We acknowledge that the number of cirrhotic patients is small, however, our data indicate that patients with cirrhosis and cured HCV/HBV infections may be at a lower risk of fatality than those with metabolic cirrhosis, when infected by SARS-CoV-2.

Whether recently cured HCV patients had a smaller exposure or were less vulnerable to COVID-19 due to possible background cellular immunity deserves further investigation. The results we have discussed here, although limited to the regions involved in our collaborative projects, are representative of geographical areas with both high and low COVID-19 prevalence.

Table 1 Baseline characteristics and laboratory findings of 332 patients hospitalized with coronavirus disease 2019 in three Italian hospitals

Factor	Total 332 patients
Age in yr, median (range)	71.9 (19-100)
Male, *n* (%)	178 (59.7)
BMI in kg/m^2, mean (range)	26.6 (17-42.7)
Arterial hypertension, *n* (%)	97 (29.2)
Glucose levels in mg/dL, mean (range)	109.4 (48-505)
Baseline ALT levels in U/L, median (range)	39.1 (4-429)
ALT of > 40 U/L, *n* (%)	74 (25.8)
Baseline AST levels in U/L, mean (range)	44.7 (7-817)
ALT of > 60 U/L, *n* (%)	82 (28.7)
Liver cirrhosis, *n* (%)	10.0 (3.0)
Baseline WBC count as × 10^9/L, mean ± SD	8.14 ± 6.28
Neutrophil count as × 10^9/L, mean ± SD	7.37 ± 10.84
Lymphocyte count as × 10^9/L, mean ± SD	1.54 ± 3.03
Lymphocyte count < 1000 as × 10^9/L, *n* (%)	160 (50.3)
Platelet count as × 10^9/L, mean ± SD	227.1 ± 107.5
Total bilirubin in mg/dL, mean (range)	0.79 (0.5-37.0)

BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; SD: Standard deviation; WBC: White blood cell.

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