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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Most current article

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Correlation Between Liver Function Tests Abnormalities and Interleukin-6 Serum Levels in Patients With SARS-CoV-2 Infection

Dear Editors:

We have read with interest the paper by Singh et al[1] reporting a high risk for hospitalizations and mortality in patients with chronic liver disease affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. SARS-CoV-2 is frequently associated with elevation in liver function tests, including alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT).[1–3] Vascular endothelium, smooth muscle cells, and cholangiocytes express the angiotensin-converting enzyme 2 receptor, which is used by SARS-CoV-2 to enter the cells, suggesting that liver involvement may be due to direct viral damage.[4,5] Singh et al hypothesized drug-induced liver injury, hypoxia, or immune dysfunction as the cause of liver tests abnormalities in patients with chronic liver disease.[1] A contribution of SARS-CoV-2–related systemic hyperinflammation to liver injury is plausible, although this has not been proven so far.

Thus, we collected data on liver tests (ALT; GGT; alkaline phosphatase; total bilirubin) and IL-6 serum levels of 80 hospitalized patients tested SARS-CoV-2 positive (real-time polymerase chain reaction on nasopharyngeal swabs) at the Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome. All patients were treated with antivirals (lopinavir/ritonavir or darunavir/ritonavir) plus hydroxychloroquine; those receiving anti-IL-6 agents or with preexisting chronic liver disease were excluded.

Liver test abnormalities defined as an ALT of >45 IU/L or GGT of >31 IU/L were observed in 25 of 80 (31.2%) and 47 of 80 (58.8%) of patients, respectively. Alkaline phosphatase elevation was present in 4 patients and bilirubin elevation in none.

Higher median serum levels of IL-6 were observed in patients with ALT (157.4 ng/L [60–1019.6 ng/L] vs 21.9 ng/L [8.7–89.1 ng/L]; $P < .0001$) or GGT elevation (82.6 ng/L [25.9–515.4 ng/L] vs 14.5 ng/L [6.9–33.8 ng/L]; $P < .0001$; Figure 1). Indeed, a significant correlation between IL-6 and ALT (Spearman's coefficient 0.515; $P < .0001$) as well as GGT (Spearman's coefficient 0.457; $P < .0001$) was found.

The highest median expression of IL-6 was observed in patients with more severe disease requiring intensive care (355.6 ng/L [172.1–1379.1 ng/L] vs 29.7 ng/L [9.75–82.95 ng/L]; $P = .0001$). In these subgroup of patients, alterations in liver function tests were also more frequent (ALT 11/17 [64.7%], $P = .002$; GGT 16/17 [94.1%], $P = .0007$).

We further explored if there was any difference between IL-6 and liver function tests abnormalities in the early (<7 days after symptoms onset) or late (>7 and <15 days after symptoms onset) phase of SARS-CoV-2 disease. ALT or GGT elevation was more common in phase 2 (ALT > upper limit of normal phase 1: 8/45 [17.8%] vs phase 2: 17/35 [48.6%], $P = .004$; GGT > upper limit of normal phase 1: 20/45 [44.4%] vs phase 2: 27/35 [77.1%], $P = .006$). IL-6 median values were also higher in phase 2 than in phase 1 (175.2 ng/L [37.5–989.6 ng/L] vs 21.8 ng/L [9.2–52.6 ng/L]; Figure 1). No case of severe hepatitis or cholestatic injury was observed.

Our data demonstrate a correlation between liver function tests abnormalities and IL-6 serum levels, proving that liver injury follows to the course of the systemic inflammatory response.

SARS-CoV-2 related disease (COVID-19) may evolve through different phases. While in the initial stage, viral symptoms are predominant and a subgroup of patients progresses to pneumonia and hyper-inflammation, characterized by a cytokine storm syndrome with systemic organ involvement.[6] At this stage, IL-6 is overexpressed and has been associated with adverse clinical outcomes.[7]

In our series, circulating IL-6 was elevated in patients with ALT or GGT abnormalities. Furthermore, patients in the late phase of COVID-19 had an increased prevalence of liver tests abnormalities and higher levels of IL-6 compared with those in the early phase. We also found an increased prevalence of AST or GGT elevation and higher IL-6 serum levels in patients requiring intensive care, confirming the association between liver injury, hyperinflammation, and COVID-19 disease severity.

In conclusion, we can argue that liver function tests abnormalities are prevalently owing to liver involvement as an "innocent bystander" in SARS-CoV-2–related inflammatory syndrome, especially in the late phase of COVID-19. Patients with chronic liver disease could be severely affected by this cytokine storm, as supposed by Singh et al.[1]

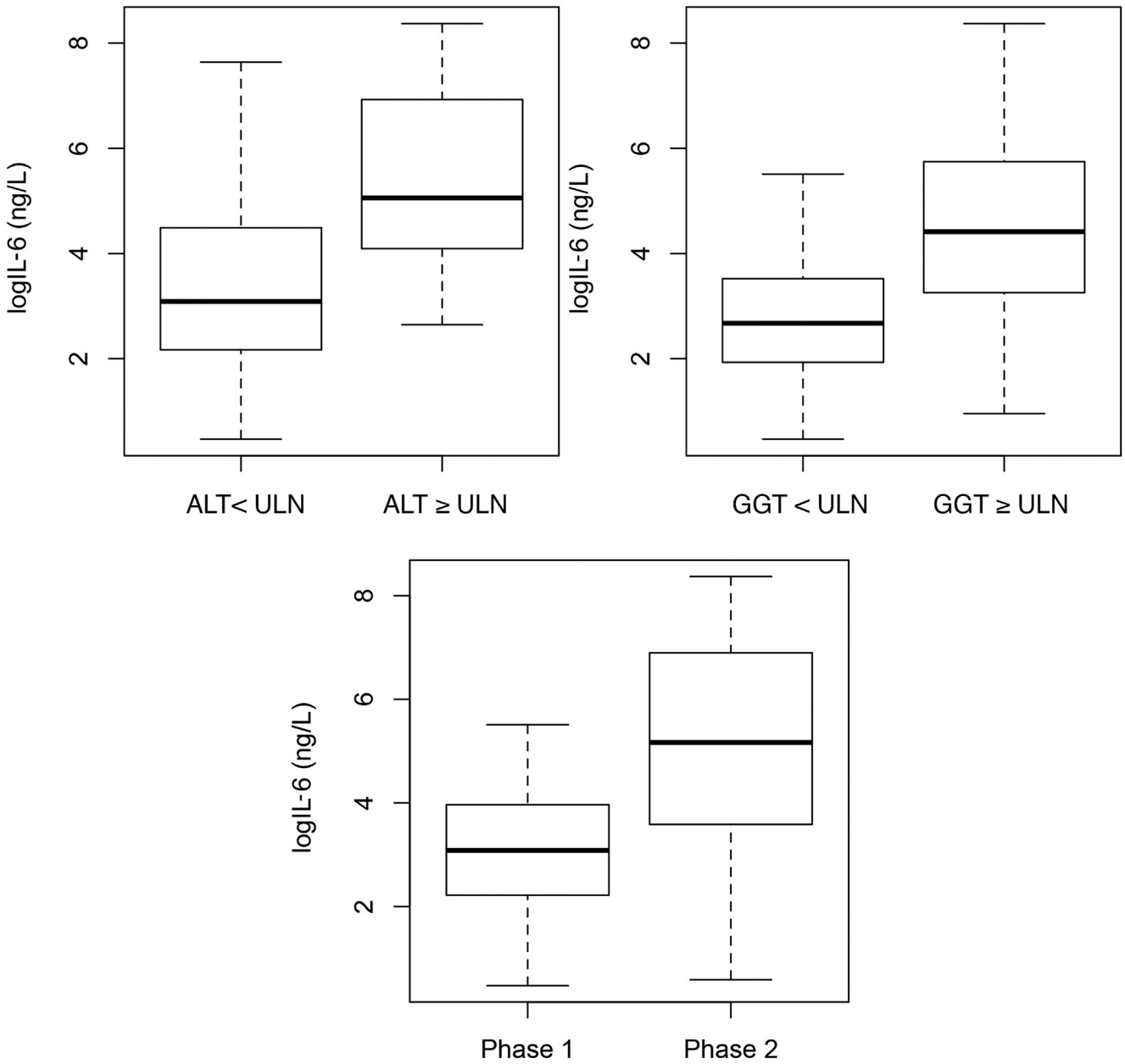

Figure 1. IL-6 median serum levels in patients with abnormal liver tests (upper limit of normal [ULN]: alanine aminotransferase [ALT] 45 IU/L, gamma glutamyl transferase [GGT] 31 IU/L) and in phase 1 (<7 days after symptoms onset) or 2 (>7 or <15 days after symptom onset) patients. Log-transformed data are reported; black bars and boxes indicate median values and interquartile ranges, whiskers the minimum and maximum.

However, the prevalence of SARS-CoV-2 infection among these patients is low and only retrospective data from electronic medical records are available; this factor makes it difficult to conduct specific investigations and, consequently, to draw definitive conclusions.

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Impact of Preexisting Chronic Liver Disease on the Outcome of Patients With COVID-19 Disease

Dear Editors:

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 patients with Coronavirus Disease 2019 (COVID-19). 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 multicentric large database. However, certain issues in the study merit close attention.

First, severe acute respiratory syndrome coronavirus 2 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 and 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/μL), which could represent greater immune-suppression in patients with COVID-19 with underlying CLD than controls. Some postulation earlier 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.

Second, the term "CLD" constitutes a spectrum of patients with varying prognosis ranging from chronic hepatitis, cirrhosis, and 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 patients with CLD 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 patients with COVID-19 with underlying CLD with regard to cirrhosis or no-cirrhosis and stratify results according to the stages of cirrhosis.

Third, most 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 nonalcoholic fatty liver disease (NAFLD) were recently shown to have progressive course, higher hepatic dysfunction, and prolonged viral shedding among patients with COVID-19.[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, the separate effect of underlying nonalcoholic fatty liver (NAFL) or NASH on the outcome was not available in that study.[4] Because 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 2 separate phenotypes on the outcome in patients with COVID-19. Recent data also suggested the effect of age on the impact of metabolic-dysfunction-associated fatty liver disease 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]

Fourth, despite propensity score matching, the patients with COVID-19 with underlying CLD had higher chronic respiratory and chronic kidney disease as compared with controls ($P = .01$). On the contrary, D-Dimer levels were higher in controls (2.9 vs. 1.0 μg/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.

Last, there were 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 contact with a health care organization. The post hoc statistical power of comparisons was acceptable at the 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 patients with COVID-19.