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.

In general, patients admitted with acute upper GI bleeding should undergo early endoscopy within 24 hours of presentation.[3] However, by practice, the priority has still been given on conservative management for patients presenting with GI bleeding. Patients are started on intravenous fluids and proton pump inhibitors. Octreotide infusions are given to patients with suspected or known liver disease while the coagulopathies are corrected. Patients are usually put to nothing per orem and blood transfusion is facilitated as necessary. With these measures, the clinical condition of patients and their hemoglobin levels are frequently assessed. Unfortunately, no specific guideline exists in the treatment of GI bleeding during the pandemic, but by practice, the basic principles of resuscitation and optimizing medical management are observed.[4] In addition, no concrete guideline has set any threshold for doing the endoscopy in patients presenting with GI bleeding, but it is generally recommended if a patient does not respond to conservative management within 24 hours. However, this threshold can be arbitrary based on emerging experience.

The timing of endoscopy is controversial, as the available evidence varies on pre-pandemic studies. Although most studies favor early endoscopy, there are some that have described on poorer outcomes. A recent study by Lau et al[5] showed that delaying endoscopy for 24 hours does not affect 30-day mortality compared with doing earlier endoscopy.[5] Similarly, a case series by Cavaliere et al[6] has shown that 6 patients with COVID-19 responded to conservative management and did not require an endoscopic procedure during their clinical course.[6] Given this dilemma in the endoscopic management of GI bleeding, aside from clinical judgment, we think that decisions could be better made using prognostic tools such as the Glasgow-Blatchford score for the pre-endoscopic risk stratification of patients.[7]

Unfortunately, COVID-19 will be with us for a long time and it will continue to have its deleterious effects on GI bleeding management. There will definitely be cases of GI bleeding in the clinics, but to avoid unnecessary risks of viral exposure on early endoscopy, we suggest going back to the basic principles of optimizing conservative management up to 24 hours. Exceptions to this are cases of severe bleeding in which clinical judgment dictates a more aggressive management or if the patient is at high risk of further bleeding or death based on risk stratification. With the latter, we suggest on future studies regarding the use of these tools in the context of the pandemic, as it may be the triaging model we are missing in this dilemma.

ENRIK JOHN T. AGUILA
IAN HOMER Y. CUA
NIKKO THEODORE V. RAYMUNDO
Institute of Digestive and Liver Diseases
St. Luke's Medical Center
Global City, Philippines

References

1. Kim J, et al. Gastroenterology 2020;159:1155–1157.
2. Filho ECC, et al. Gastrointest Endosc 2020;92:440–445.e6.
3. Barkun AN, et al. Ann Intern Med 2019;171:805–822.
4. Sethi A, et al. Clin Gastoenterol Hepatol 2020;18:1673–1681.
5. Lau JYW, et al. N Engl J Med 2020;382:1299–1308.
6. Cavaliere K, et al. Gastrointest Endosc 2020;92:454–455.
7. Sung JJY, et al. Gut 2018;67:1757–1768.

Conflicts of interest
The authors disclose no conflicts.

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Reply. We thank Aguila et al for their interest in our article and appreciate their perspective on the management of gastrointestinal bleeding during the coronavirus disease 2019 (COVID-19) pandemic.

We agree that the pandemic has caused significant dilemmas for risk-stratification of patients presenting with gastrointestinal (GI) bleeding. The risks of staff exposure and depletion of personal protective equipment need to be weighed against the benefits of endoscopy on a case-by-case basis using clinical judgement. As reported in our study, conservative medical management, including blood product transfusions and proton pump inhibitor use, was emphasized early in the pandemic and inpatient endoscopy volume significantly decreased.[1]

A recent study by Blackett et al[2] found that, among patients undergoing endoscopic procedures in New York City hospitals during the first wave of the pandemic, COVID-positive patients were more likely to have an indication of GI bleeding at 41.7% compared with 29.8% of COVID-negative patients and 24.1% of untested patients. Endoscopies in COVID-positive patients were also more likely to have a hemostatic intervention compared with COVID negative patients (adjusted odds ratio, 2.90; $P = .041$). These findings likely reflect the higher clinical threshold to pursue endoscopy in COVID-positive patients.

A recent randomized trial found that delaying endoscopy for $\leq$24 hours does not affect 30-day mortality compared with earlier endoscopy,[3] but it is difficult to adapt these guidelines during the pandemic because patients seem to be presenting later in their disease course. In another study from our institution by Laszkowska et al,[4] the presence of GI symptoms in COVID-positive patients was associated with a longer time from symptom onset to presentation for admission compared with COVID-positive patients without GI symptoms (median, 7.4 days vs 5.4 days; log-rank $P <$ .01). In our study, we found that patients with GI bleeding during the pandemic presented with more severe laboratory abnormalities, which may reflect patients' reluctance to seek medical care unless symptoms worsen. The ongoing COVID-19 pandemic has presented new challenges in the management of GI bleeding, and future studies are needed to develop evidence-based guidelines relevant to this specific population.

JUDITH KIM
Division of Digestive and Liver Diseases
Department of Medicine
Columbia University Irving Medical Center
New York, New York

JOHN B. DOYLE
BENJAMIN LEBWOHL
Division of Digestive and Liver Diseases
Department of Medicine
Columbia University Irving Medical Center
New York, New York

References

1. Kim J, et al. Gastroenterology 2020;159:1155–1157.
2. Blackett JW, et al. Dig Dis Sci 2020;15:1–10.
3. Lau JYW, et al. N Engl J Med 2020;382:1299–1308.
4. Laszkowska M, et al. Clin Gastroenterol Hepatol 2020 Sep 30;S1542-3565(20). 31367-7.

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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]