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Should Anal Swab be Obtained Instead of Throat Swab? Gastrointestinal Complaints and Findings in The Course of COVID-19

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ABSTRACT

Aim (Background): *The gastrointestinal system (GIS) is important in diagnostic procedures screening for COVID-19. Nausea/vomiting, diarrhea, abdominal pain, and ageusia are gastrointestinal (GI) symptoms commonly recorded in the pandemic. This review aims to shed light on this important aspect of the course of COVID-19, with a special emphasis on diagnostic opportunities.*

Materials and Methods: *Currently available literature on the GI manifestations of COVID-19 was identified through searches of the available databases. Data on the characteristics, features, and outcomes associated with GI signs and symptoms, along with diagnostic opportunities and relevant comorbid states [e.g., inflammatory bowel diseases (IBD) and liver failure], were extracted from the manuscripts.*

Results: *The GIS was shown to be closely interrelated with COVID-19 in several ways. The presence and severity of GI complaints are correlated with the severity of the disease. Those with GI signs and symptoms have higher AST and ALT and coagulopathy. Those with GI signs more commonly have fever; however, they suffer from milder disease. While liver damage is associated with lymphopenia, neutropenia and male sex, it has been observed that AST is associated with mortality in COVID-19 patients. IBD does not pose a high risk for COVID-19.*

Conclusion: *While RNA positivity in the GIS provides a major diagnostic opportunity, it also represents a dangerous situation for healthcare workers and the public in regard to fecal-oral transmission. The GIS was associated with COVID-19 in patients with chronic disorders such as liver disease and IBD.*

Keywords
Gastrointestinal complaints, COVID-19; Diagnosis, Anal swab, Liver enzymes, Fecal RNA.

Introduction

The gastrointestinal system (GIS) does not predominate among the systems affected by COVID-19. More than 15 million people around the world have been inflicted with COVID-19, officially causing more than 600,000 deaths in seven months. Dyspnea, fever, and dry cough are most commonly recorded in individuals with verified COVID-19, followed by muscle/joint pain, headache, nausea/vomiting, diarrhea, cerebrovascular symptoms, anosmia, etc., with considerable variations between countries and regions as well as temporal differences during the pandemic.

The GIS is important in diagnostic procedures screening for COVID-19 in a given patient. SARS-CoV-2 RNA can be found throughout the GIS, and thus in the feces, in a longer time window than in the respiratory tract. RNA positivity continues to be present in feces in individuals with very few symptoms, even in asymptomatic individuals. RNA positivity in the GIS and feces is a diagnostic opportunity and indicates a dangerous situation for healthcare workers carrying out procedures (e.g., endoscopy, rectoscopy, digital rectal examination, etc.), household members and the public in regard to fecal-oral transmission.

The GIS has also been associated with COVID-19 for patients with chronic disorders of the GIS, including liver disease, inflammatory bowel diseases (IBD) and others.

This review aims to shed light on this important aspect of the COVID-19 clinical course, with a special emphasis on diagnostic opportunities related to the GIS.

Materials and Methods

Currently available literature on the GI manifestations of COVID-19 was identified through searches of the available databases. Data on the characteristics, features, and outcomes associated with GI signs and symptoms, along with diagnostic opportunities and relevant comorbid states [e.g., inflammatory bowel diseases (IBD) and liver failure], were extracted from the manuscripts.

Results

GIS and the pathophysiology of the virus

SARS-CoV-2 shows affinity for every cell that contains ACE2 receptors. Since these receptors are abundant in the GIS, these tissues can host the virus. The virus is excreted abundantly via feces during acute illness, mostly in severe patients. Fecal-oral transmission occurs in 10% to 53% of patients. The most important aspect of the GIS in the diagnosis of COVID-19 is that RNA positivity in feces continues much longer (up to 50 days) than in respiratory tract samples (maximum 14 days) [1].

It is known that the SARS virus can be found in the feces/small intestine from the 7th day in animals, but the virus located directly in the stomach do not cause disease (Nagata et al. 2020). In specific relation to this, an interesting study revealed that viral RNA positivity was also evidenced in urban wastewater [2].

Which GI findings do we mention?

GI findings are commonly recorded in patients with COVID-19, although they are not regarded as the so-called “main symptoms” (fever, shortness of breath, persistent dry cough). Abdominal pain, diarrhea, nausea, vomiting, and a loss of appetite and the sense of taste (ageusia) are the most common GI complaints [3] (Figure 1). Although GI complaints are generally considered to be among the “atypical symptoms” in individuals with COVID-19, they can represent an important adjunct to the main findings and help in the diagnosis of the disease. In rare cases, GI symptoms may ensue as the main complaint or finding on presentation to the hospital. Atypical or infrequent findings may also lead to difficult recognition of patients and longer hospital stays.

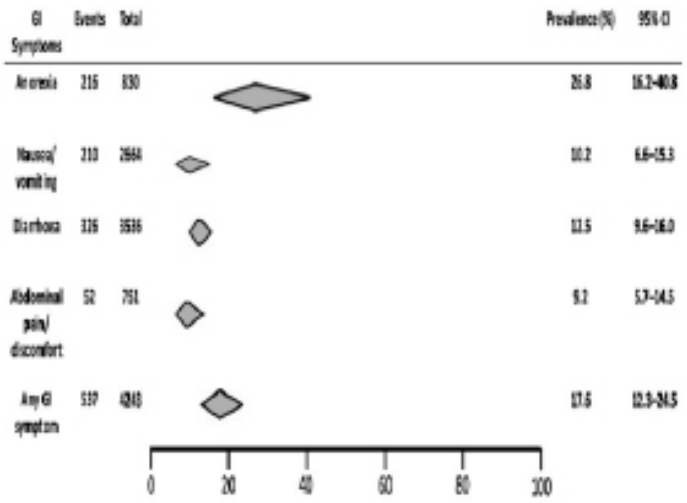

Figure 1: In their meta-analysis, Cheung et al. reported concrete evidence on the rates of GI complaints in patients with COVID-19 [3].

When 1141 patients were analyzed in the beginning of the epidemic in China, it was reported that 183 (16%) presented with GI complaints [4]. The most frequently reported among them were a loss of appetite, nausea and vomiting, diarrhea and abdominal pain (Table 1). As a rule, this group of patients had leukopenia, lymphopenia, increased CRP, and elevated liver enzymes, whereas kidney function was normal. In 96% of patients, there was evidence of infection in chest tomography; therefore, it was a group of patients considered to have severe COVID-19.

Table 1: Possible GI complaints in patients diagnosed with COVID-19 in order of frequency and laboratory findings primarily in patients presenting with GI complaints [4].

Complaints	Laboratory findings
Loss of appetite	Leukopenia (mean 2.7x 109/L)
Nausea	Lymphopenia (avg. 0.53x 109/L)
Vomiting	CRP increase
Diarrhea	Liver enzyme elevation
Abdominal pain	Normal kidney functions

Ghoshal et al. published a systematic review and cited that GI symptoms were found in the whole case pool at a rate of 17.6%, similar to that published by Luo et al. [5]. Studies reporting that patients with GI complaints have a worse clinical course are also found in the literature.

In a study in which COVID-19 patients in Hubei were analyzed, respiratory symptoms were reported in the majority of the patients (89%), but every second patient complained of GI symptoms [6]. Among the GI complaints, the most common complaints were a loss of appetite (78%), diarrhea (34%), vomiting (4%), and abdominal pain (2%). It is interesting to note that 3% of individuals presented with only GI complaints without respiratory symptoms.

GI complaints increase in parallel with the severity of the disease. Higher liver enzymes (AST and ALT), prolonged PT and monocytopenia were found in those with GI findings and complaints. Another important point is that patients with GI findings present later than those with respiratory complaints; thus, their recognition and management lag behind others.

Analyzing a series of 157 patients in two hospitals from Hubei, Cao et al. reported at least one GI complaint and/or finding in 40% of the sample [7]. The most frequent, a loss of appetite (75%), nausea (33%) and diarrhea (40%), were recorded among the GI findings. No difference in terms of age, sex, or comorbidities was observed between those with and those without GI findings. Interestingly, those with GI signs and symptoms experienced less severe disease (12.7% vs. 35.1%).

In a systematic review of 38 studies, de Souza et al. reported that diarrhea was observed in 8.1% of patients, and nausea and vomiting were observed in 7.1% of patients [8].

Viral RNA positivity in feces

Coronaviruses have been found in feces since the 1980s. Although rotaviruses and some adenoviruses are famous in this regard, it is thought that up to 70% of "enteric viral particles" may be coronaviruses. It has been reported in many studies that viral RNA continues to exist in fecal samples until after respiratory symptoms have been normalized.

Some researchers have reported that COVID-19 patients have no virus in feces samples. However, in new studies, the presence of enteric virus is widely accepted in patients with COVID-19 [9,10].

In a cohort analysis of 59 patients in Hong-Kong, Cheung et al. found that 25% of the patients with SARS-CoV-2 had GI complaints, and RNA positivity was found in 38.5% of patients with diarrhea and in 8.7% in those without diarrhea (p = 0.02) [3]. It is interesting to note that fever was reported in 100% of the individuals with GI complaints. In the meta-analytical study, 17.6% of patients had GI complaints, but interestingly, the viral positivity in feces was 48.1% (Figure 2). Additionally, 70% of those with fecal positivity were individuals in whom respiratory samples had become negative.

In Korea, viral RNA positivity in feces during the quarantine period was shown to have lasted up to 50 days and can be identified in patients without any GI complaints [11].

Ahmed et al. published the cases of three adults (40, 44 and 53 years old) who presented with abdominal findings mimicking acute surgical abdomen and were diagnosed with COVID-19 [12]. The patients did not require surgical intervention. Although all three individuals had COVID-19 pneumonia, one of them had epiploic appendagitis, one had lower lobe pneumonia, and the other had nonspecific abdominal pain.

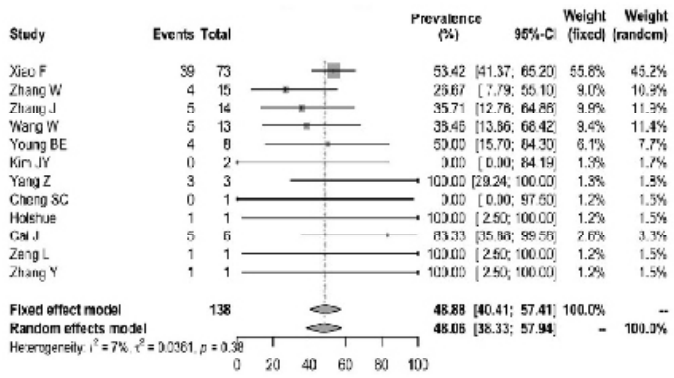

Figure 2: RNA positivity rates in feces in various studies [3].

Pediatric viral positivity in feces

In a series consisting of 5 symptomatic and 5 asymptomatic 10 children in China, viral RNA positivity was not interrupted after discharge in 7 children diagnosed with COVID-19 [13]. In respiratory samples, the median duration of viral RNA positivity was 9 days, while it was 34.4 days in fecal samples.

RNA positivity in anal swab samples

Even when nasopharyngeal swab samples are negative, viral RNA can remain positive in feces. Zhang et al. found more RNA positivity in anal swab samples than in throat swab and blood samples [14]. Especially in the late period of the disease, anal swab sample positivity becomes even more prominent. This issue is important in terms of fecal-oral contamination.

Another patient, a 63-year-old woman, presented with bloody diarrhea, vomiting, and abdominal pain [16]. Pulmonary lesions in the CT scan of the abdomen in this patient, who had a history of rheumatoid arthritis and Sjogren's disease (Figure 4).

GI complaints in children with COVID-19

In China, an analysis of 182 children with COVID-19, with a median age of 6 years, revealed that fever and cough were the two most common complaints (43% and 44%, respectively) [13]. In 11% of the children, GI symptoms were recorded, and most of them were diarrhea, abdominal discomfort and vomiting.

Mao et al. published a meta-analysis on this subject and reported that children and adults with COVID-19 presented at the same rate, with up to 10% with GI signs and symptoms but without

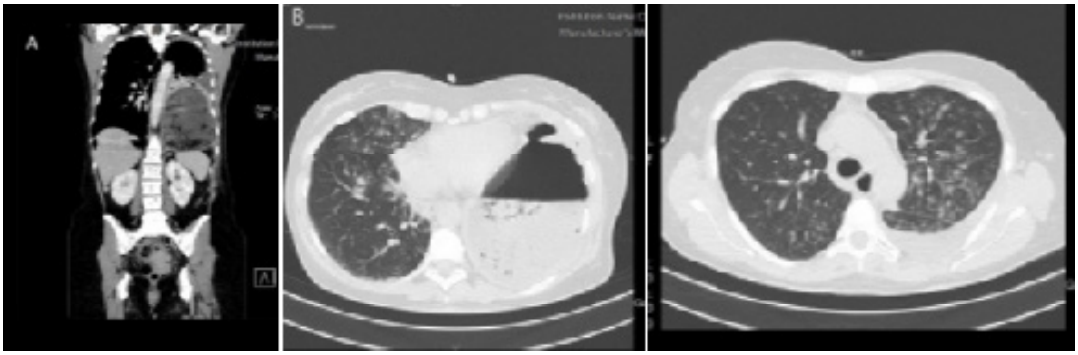

Figure 3 depicts tomographic images of a young Italian woman with COVID-19 pneumonia who was eventually diagnosed with gastric perforation with diaphragmatic rupture after 5 days of fever and dry cough [15] (Figure 3).

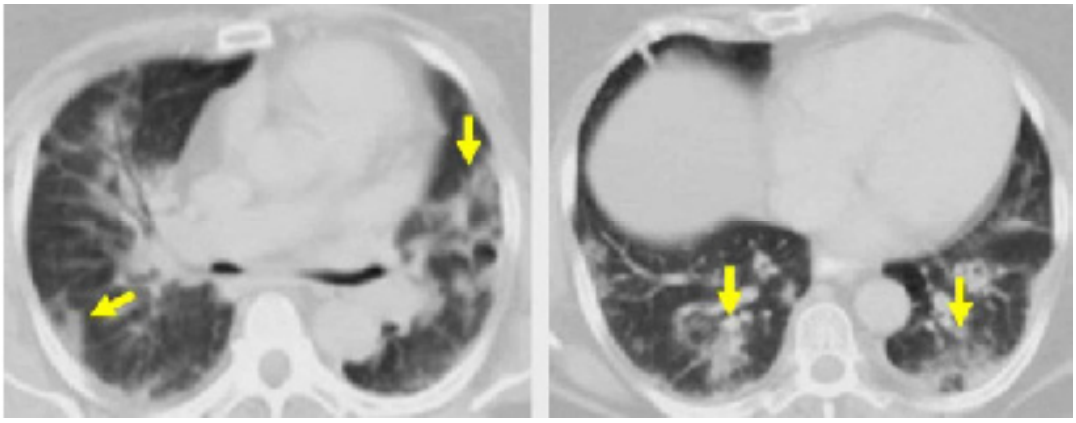

Figure 4: Bilateral ground-glass ground opacities in a 63-year-old woman with a history of rheumatoid arthritis and Sjogren's disease presenting with bloody diarrhea, vomiting, and abdominal pain. Ground-glass opacities are typical for COVID-19.

respiratory complaints [17] A total of 97.8% of children had a mild clinical course. The presence of intussusception and sepsis in the only child who died revealed the vital importance of GI symptomatology.

Inflammatory bowel diseases (IBD) and COVID-19

Treatment with anti-inflammatory drugs including corticosteroids, immunosuppressants and biological agents, are the mainstay therapies in the management of IBD. This prompts a belief towards a consideration of IBD patients as a high-risk group in the pandemic era [18]. This is mostly due to anti-TNF-α treatment or other immunosuppressants administered to IBD patients.

Very few studies specific to this subject are reported, and limited data have been collected. In a study that analyzed 12 patients who had COVID-19 among 1918 IBD patients, it was noted that most of the COVID-19 patients (3/4) were female, and the mean age was 52 [19]. Two of three patients diagnosed with COVID-19 had to be admitted to the hospital. The most common complaint (75%) was diarrhea. The mean daily stool frequency was 5.4 times. More importantly, the presenting symptom associated with COVID-19 in 5 patients (42%) was diarrhea. Diarrhea was the only symptom in 2 patients (17%). It was reported that diarrhea was triggered by the initiation of HCQ or lopinavir/ritonavir in 4 patients in whom diarrhea was seen after hospitalization and healed with the discontinuation of the drug.

In Spain, an incidence of COVID-19 of 6.2% has been reported in 1000 patients with IBD. Since this value is 6.6% in the general population, it is thought that IBD may have had a protective role (OR = 0.74). The mortality rates associated with COVID-19 in patients with IBD do not differ from those in the general population. The standardized mortality risk is similar to that of the general population, with 1 death/1000 people.

It has been reported that only 4 out of the 1500 IBD patients who were being followed up in two large hospitals in Greece by taking some precautions in hospitals and in society have had COVID-19 [20].

Taxonera et al. devised a follow-up system based on telephone consultations instead of face-to-face visits for patients with IBD [21]. The rate of IBD-related hospitalization and visits to the emergency department decreased by 50% and 58%, respectively, compared with rates in the same period the previous year.

Will there be a change in treatment? Both yes and no

SARS-CoV-2 infection is not opportunist; it has high contagiousness and affects healthy people as well as those with comorbidities. Therefore, there is no essential change in management [22,23]. Anti-TNF therapy, used in the treatment of IBD, can lead to an increased risk of infection [24]. International organizations have also suggested that immunosuppressants and biological agents should be discontinued in individuals with COVID-19 [25,26].

In conclusion, IBD per se does not convey a high risk for COVID-19, and diarrhea requires attention as the most common complaint. Additionally, physicians should bear in mind that the patient may be diagnosed with COVID-19 even if the sole or main symptom is diarrhea in patients with IBD. Immunosuppressant agents should be discontinued.

Liver disease (LD) and COVID-19

Individuals with liver disease are identified as an important subgroup of patients with COVID-19, although reports are rare. Chronic liver disease (CLD) has been reported at a rate of 1.4% in large series [27]. The most common LD in COVID-19 patients is hepatitis.

Although numerous articles have been published in the pandemic era, the exact cause of liver injury has not been clarified, nor is there clear evidence of the interaction between liver injury and COVID-19. Wu et al. cited that ACE2 receptors play a pivotal role in the damage of not only the type II alveolar cells but also liver cells, specifically bile duct cells, because of the expression and intensity of ACE2 receptors in these cells [28]. They also put forth that drug-induced hepatotoxicity or liver injury are noted commonly in patients surviving from COVID-19, as manifested by elevations of liver enzymes.

In asymptomatic individuals, mild liver damage with ALT, AST and GGT elevations can be noted in 10 to 50%. A low degree of hyperbilirubinemia may be observed, and the physician can notice this with yellow color in the sclerae and a darkening of urine color. Mild liver damage does not require any specific treatment. Rarely, liver damage can lead to acute liver failure.

Relationship between liver failure and COVID-19 severity

Parohan et al. showed that elevations in AST, ALT, and total bilirubin and low levels of albumin were associated with severe COVID-19 courses (WMD, 8.8, 7.3, 2.3, and -4.2, respectively) [29].

In July 2020, Mao et al. published a meta-analysis of 35 studies involving 6686 patients. They reported that abnormal liver function was seen at a rate of 19%, and ALT and AST elevation were associated with a severe COVID-19 course (OR = 1.89 for ALT, 3.08 for AST) (Mao et al. 2020). Patients originating from Hubei presented with liver disorders more commonly than others ($p < 0.0001$). Patients presenting with GI complaints were admitted later than the others. At the same time, this group is at higher risk for ARDS development (OR = 2.96) and poor prognosis. No increased risk for mortality was reported.

The elevation of liver enzymes is commonly seen in patients with COVID-19, more prominently as the disease becomes more severe. In a retrospective multicenter study involving more than 5700 adults with COVID-19 pneumonia in Hubei, Lei et al. reported that AST is particularly closely related to mortality risk among all indicators of liver damage [22]. Liver damage indicators are mostly associated with lymphopenia, neutropenia and male sex.

The authors emphasized that AST values should be monitored closely, especially in inpatients, because of such a relationship. The AST median was 22 U/L in nonsevere COVID-19 patients, while the corresponding figure was 31 U/L in severe COVID-19 patients ($p < 0.001$). Liver damage was detected an average of 17 days after COVID-19 findings appeared.

Does pre-existing chronic liver disease have an impact on the course of COVID-19?

Some studies investigating this specific interrelationship between LD and COVID-19 are found in the literature. Sarin et al. conducted the APCOLIS Study (APASL COVID-19 Liver Injury Spectrum Study) [30]. The research revealed that liver-related complications increased significantly with the stage of LD; a Child-Turcotte-Pugh score of 9 or more on admission predicted high mortality in the course of COVID-19 (Figure). A high mortality rate (43%) was remarkable in decompensated cirrhotic patients. High bilirubin and a high AST/ALT ratio are also strong predictors of mortality of patients with CLD. SARS-CoV-2 infection gives rise to substantial liver injury in CLD patients, with decompensated cirrhosis in one-fifth of CLD patients, and worsens the clinical status of all with CLD.

Does liver failure (LF) occur in patients with COVID-19?

Yes. Severe COVID-19 causes multiple organ failure as well as respiratory distress. A close relationship exists between severe disease and LF. In this regard, Samidoust et al. published a meta-analysis including 4191 patients with COVID-19. Among 288 COVID-19 cases that resulted in death, LF was recorded in 22.8% [31]. Liver damage is more frequent and more severe in severe patients than in mild patients.

Does elevated liver function (enzymes) or cirrhosis alter COVID-19 therapy?

Generally, no. Drugs commonly used in the treatment of COVID-19 (chloroquine, hydroxychloroquine, favipiravir, lopinavir/ritonavir, remdesivir, tocilizumab, statins and azithromycin) do not cause liver injury; therefore, they can be given if indicated in a given patient.

In general, immunosuppressive treatment is also administered as required in patients who are in the queue for a liver transplant or in those who have received a transplant.

Summary and Conclusion

The GIS is closely related to COVID-19 in several ways:

- Patients with GI complaints are admitted and hospitalized later than those with respiratory findings.
- The presence and severity of GI complaints are also correlated with the severity of the disease. Those with GI signs and symptoms have higher AST and ALT, coagulopathy (prolonged PT) and monocytopenia.
- In individuals with COVID-19 (if a loss of appetite is excluded), GI complaints are seen at a rate of 16-40%. Interestingly, those with GI signs more commonly have fever; however, they suffer from less severe disease.

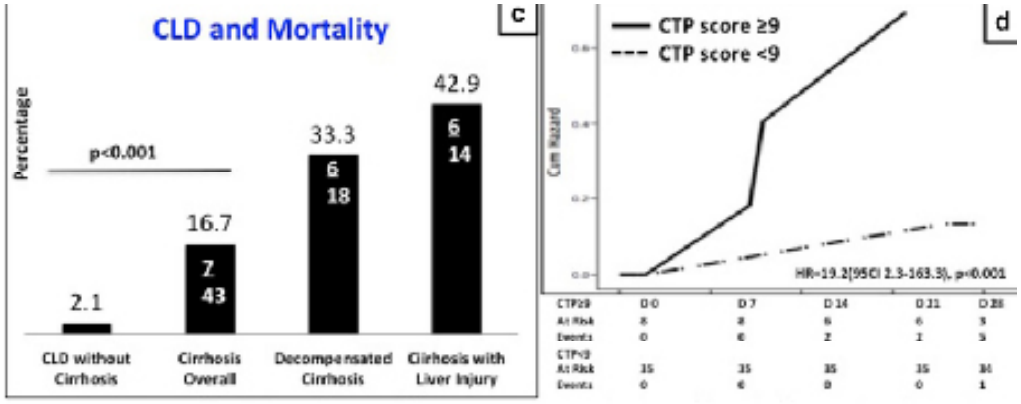

Figure 1: The mortality increased significantly with SARS CoV2 infection among cirrhotic patients compared with those without cirrhosis ($p < 0.001$) and with decompensation. The mortality is highest (43%) in the spectrum with the onset of liver damage. Among cirrhotic patients exposed to SARS CoV2 infection, the outcome was poor, with a Child-Turcotte-Pugh (CTP) score of 9 or more [AUROC 0.94, sensitivity 86% and specificity of 94%, HR = 19.2 (95 CI 2.3–163.3), $p < 0.001$] [30].

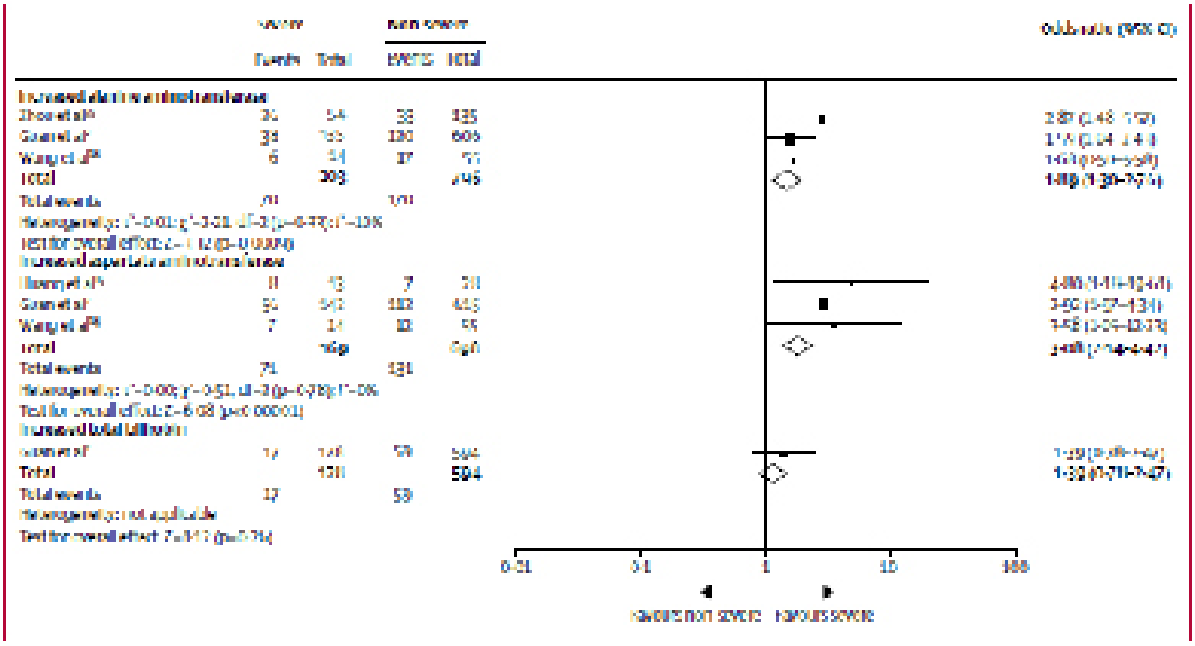

Figure 2: The relationship between elevations in liver enzymes and severe disease has been demonstrated through a meta-analysis [22].

- SARS-CoV-2 RNA positivity in the GIS, and thus in the feces, persists longer than in the respiratory system, especially in late-stage patients and after discharge. Infection continues in feces in individuals with few symptoms or in those who are asymptomatic.
- RNA positivity in the GIS and feces is a diagnostic opportunity and indicates a dangerous situation in terms of fecal-oral transmission.
- Risks for nosocomial transmission and healthcare professionals are also present in the hospital environment, and better protection is required in procedures such as endoscopy and rectoscopy.
- When it is assumed that the COVID-19 pandemic will not disappear rapidly, the feasibility of viral nucleotide scans of anal swab or fecal samples will be discussed.
- Elevated levels of ALT are frequently seen in individuals with COVID-19, especially as the disease becomes more severe. It has been observed that AST is especially associated with mortality.
- Liver damage is most commonly associated with lymphopenia, neutropenia and male sex in COVID-19 patients.
- IBD per se does not pose a high risk for COVID-19, and diarrhea is the most common complaint in these patients.
- Most patients with IBD and liver diseases can be managed remotely using technological advances. This approach can also help increasing patient satisfaction amid pandemic. For example, hospitals can arrange telephone consultations to ensure a minimum standard quality of care while expediting diagnostic and therapeutic measures.

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