

Thursday, July 22, 2021

Subrata Ghosh, MD
Editor-in-Chief
Andrzej S Tarnawski, PhD
Editor-in-Chief
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Dear Dr. Ghosh and Dr. Tarnawski,

Thank you for providing important comments regarding our “Covid-19 Status Quo: Emphasis on Gastrointestinal and Liver Manifestations” invited review (Manuscript NO: 67601).

As instructed, we are submitting both tracked changes and clean formatted manuscripts. We have considered the reviewers’ feedback very carefully and have addressed all of the points.

We look forward to your response and hope we can contribute to your highly regarded journal.

Best Regards,



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Responses to Reviewers' Comments

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This is an interesting review concerning the impact of COVID-19 disease on gastrointestinal and liver dysfunction. However,

- Thank you for your kind words.

The manuscript also has the following points that can be improved:

1. Although the authors have concluded that the structure and shape of gastroenterology departmental activity is changing, also the change of endoscopy practice, no details are mentioned in the manuscript about these. Please add.

- Thank you for your comments and we have revised **Paragraph 2, page 12** to include additional comments with references regarding the structure and shape of the gastroenterology department activity. Paragraph now reads;

The pandemic has prompted a change in structure and shape of gastroenterology departmental activities. 27% of the centers in the United States and Canada had implemented routine endotracheal intubation for upper endoscopic procedures [87]. The reshaping has been aimed to address urgent and emergent needs of the community and decreasing patient exposures in the hospital. Most of the practices had altered coverage schedule for the physicians. Strict protective measures during endoscopic procedures such as gowns, gloves, face shields, N95 masks, hairnets, double gloves, shoe covers, have also been implemented [87]. The patients are screened at arrival for symptoms and exposures. During the pandemic, only highly urgent endoscopic procedures are being performed on COVID-19 patients [88]. Endoscopy should be performed only when necessary and in a negative pressure flow room for COVID-19 patients if such a room is available. Where a negative pressure flow room for COVID-19 is not possible, strict sanitation measures are recommended [89].

2. In the epidemiology section, it is sufficient to focus on the high infectivity of COVID-19 virus, while it is suggested to simplify the interpretation of R_0 and the second attack rate.

- The epidemiology section on **Paragraph 1, page 4** has been revised to simplify the interpretation of R_0 . Paragraph now reads;

The high degree of infectivity of the COVID-19 virus is attributed to its novelty in the human host. It can be measured by the basic reproduction number or R_0 , which is a statistical tool used to describe the contagiousness of a virus. It is estimated that the SARS-CoV-2 R_0 is between 2 and 3, signifying that each infected person is likely to spread the infection to 2 to 3 additional people [13, 14]. The secondary attack rate characterizes the contagiousness of a virus in the close contact setting, which considers how social behaviors may influence transmissibility [15, 16]. Jing et al. estimated the secondary attack rate of COVID-19 to be 12.4% amongst close relatives and 17.1% amongst those who share the same residential address [17].

In addition, as this review aims to discuss the gastrointestinal and hepatic manifestations of COVID-19 disease, it is recommended to discuss the impact of faecal-oral transmission.

- Thank you for your suggestion, and we have added additional comments regarding the impact of faecal-oral transmission in **Paragraph 3, page 7**. The paragraph now reads;

Gastrointestinal symptoms are common in COVID-19 [54], occurring in up to 35% of patients [39]. The most commonly reported GI manifestations are diarrhea, nausea, vomiting, and abdominal pain [55]. Loss of appetite and dysgeusia have also been described [56]. As previously mentioned, expression of the ACE2 receptor is highly prevalent in esophageal stratified epithelial cells and enterocytes within the ileum and colon providing the pathologic rationale for GI symptoms in COVID 19 [57]. Viral particles have been isolated in fecal samples suggesting the possibility of fecal transmission of the virus [58]. A minority of patients with positive stool testing lacked GI symptoms suggesting asymptomatic carriage of disease [59]. As many as 20% of patients continue to shed viral particles in stool despite absence in respiratory tract samples [39]. These findings highlight the importance of fecal-aerosol-mucosal transmission among individuals exposed to contaminated feces, including public toilets or areas with poor sanitation. This provides a concerning avenue for infectious spread in under-developed regions of the globe, including many regions in Africa and South Asia which lack comprehensive wastewater treatment facilities. Disease control guidelines have emphasized effective management and disinfection of potentially contaminated feces in COVID19 patients [45], and aggressive vaccination programs in areas at higher risk for fecal-oral spread.

3. Some references should be properly formatted and consistent.

- All references have been appropriately formatted into the National Library of Medicine (NLM) Style, including all authors and DOI, PMID, and PMCID.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: 1. In these review mention about the vaccine and mechanism

- Thank you for your suggestion, and we have revised **Paragraph 1, page 6**, to include the different vaccines according to their mechanism of action and their references. The paragraph now reads;

Human infection happens by aerosol droplets or carried on fomites. Upon inhalation, the SARS-CoV-2 enters host respiratory cells via the angiotensin-converting enzyme 2 (ACE2) receptor and activating receptors such as the transmembrane protease serine 2 (TMPRSS2) or cathepsin (Figure 1) [27,28]. Viral replication in the infected cells causes immune cells to proliferate and produce large amounts of cytokines and chemokines such as TNF-alpha, interferon-gamma (IFN-gamma), Interleukin 6 (IL-6), Interleukin 8 (IL-8), and Interleukin 10 (IL-10) (Figure 1) [28,29]. This process causes a cascade of inflammatory reactions with toxic damage to the lungs (Figure 2). These mechanisms have also been utilized as targets for therapy. After the initial focus on hydroxychloroquine, emphasis has more recently been on polymerase inhibitors (Remdesivir), binding agents such as convalescent plasma therapy and IL-6 inhibitors such as Tocilizumab [30, 31]. Vaccines, such as mRNA-based (Pfizer-BioNTech, Moderna), adenovirus-based (AstraZeneca, Sputnik V, Convidicea, ZF2001), inactivated viral particles (CoronaVac, BBIBP-CorV, Covaxin, CoviVac), non-replicating viral vector (Janssen), and peptide (EpiVacCorona) (Figure 3) [30-33] are areas of active evolution. Adenovirus based intra-nasal COVID vaccines are currently undergoing evaluation via clinical trials. These vaccines with different mechanisms of action trigger [34,35] immune responses and are of great benefit to systematically stop the COVID-19 pandemic.

2. Conclusion is clearly summarize the data that author propose

- Thank you.

3. The research still going on and we are waiting for the result from vaccine that could effect the organ especially liver and gastrointestinal.

- Thank you. We agree with the reviewer, and we have mentioned in **Paragraph 1, page 6**, that vaccine data is an area of active evolution.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The authors have aimed to review the impact of COVID-19 disease on gastrointestinal and liver dysfunction. The article does reflect some of the published data on this aspect. However, it is also true that this aspect of COVID-19 has been reviewed recently in many articles and there need to be new information in new reviews. A few specific concerns are mentioned below: 1) Authors have in their conclusion (abstract as well last para of text) mentioned about changed endoscopy practice. However, the article has not discussed the

issues related to indication, risks involved, triaging and preventive aspects of endoscopy practice anywhere in the article. 2) Similarly, while the authors have concluded that structure and shape of gastroenterology departmental activity is changing. No details are mentioned in the manuscript about the same.

- Thank you for your comments and we have revised the section titled **FUTURE DIRECTIONS AND LESSONS LEARNED, pages 11-12** to include additional comments with references regarding the structure and shape of the gastroenterology department activity.

3) Description of history of COVID-19 originating from china and discussion on case fatality ratio is well known and repetitive in all articles related to COVID-19. This can be avoided 4) Since the article aimed to discuss G.I and liver manifestations, section on virology is not really required at least in as much detail as provided. Similarly infectiousness and transmissibility of COVID-19 is also partly out of context.

- We thank the reviewer for the comments and suggestions. We would like to keep the information regarding the origins of COVID-19 as described in the introduction, the virology, and the infectiousness and transmissibility of COVID-19 in our review paper since it provides a summarized description of the events and the molecular mechanisms. We have simplified the interpretation of R0 in the epidemiology section on **Paragraph 1, page 4**. The paragraph now reads;

The high degree of infectivity of the COVID-19 virus is attributed to its novelty in the human host. It can be measured by the basic reproduction number or R0, which is a statistical tool used to describe the contagiousness of a virus. It is estimated that the SARS-CoV-2 R0 is between 2 and 3, signifying that each infected person is likely to spread the infection to 2 to 3 additional people [13, 14]. The secondary attack rate characterizes the contagiousness of a virus in the close contact setting, which considers how social behaviors may influence transmissibility [15, 16]. Jing et al. estimated the secondary attack rate of COVID-19 to be 12.4% amongst close relatives and 17.1% amongst those who share the same residential address [17].

5) Pathogenesis of liver involvement is mentioned more than once and is therefore repetitive. 6) Authors should have mentioned guideline about use of some drugs such as Remdesivir in presence of liver dysfunction and elevated liver enzymes.

- Thank you for your comments. We have revised the review article to simplified the pathogenesis of liver involvement. In addition, we have mentioned guidelines about the use of Remdesivir in the presence of liver dysfunction and elevated liver enzymes in Paragraph 2, page 10. The paragraph now reads;

Treatments for COVID-19 have been associated with elevated liver enzymes and subsequent injury, most notably with remdesivir use. Remdesivir use in early trials and series was associated with 10-50% of patients developing transient, mild to moderate (<5 times upper limit or normal) elevations in AST and ALT within 5 days of therapy. 9% of patients in reported trials showed at least moderate elevations, but resolved with

discontinuation and were not associated with clinically significant injury. Pharmacology guidelines recommend close monitoring of liver enzymes and early discontinuation of infusions if elevations rise > 10 times the upper limit of normal [74, 75]. Dexamethasone remains a treatment for severe COVID-19 infection. It should be acknowledged that prolonged use of corticosteroid therapy can cause hepatic steatosis as well as increase the risk of developing reactivation of latent infections, such as viral hepatitis B.

7) Some of references need to be put in proper style.

- All references have been appropriately formatted into the National Library of Medicine (NLM) Style, including all authors and DOI, PMID, and PMCID.

Science Editor (1):

(2) Summary of the Peer-Review Report: Authors should add details about structure and shape of gastroenterology departmental activity is changing.

- Thank you for your comments, and we have revised **Paragraph 2, page 12**, to include additional comments with references regarding the structure and shape of the gastroenterology department activity. The paragraph now reads;

The pandemic has prompted a change in structure and shape of gastroenterology departmental activities. 27% of the centers in the United States and Canada had implemented routine endotracheal intubation for upper endoscopic procedures [87]. The reshaping has been aimed to address urgent and emergent needs of the community and decreasing patient exposures in the hospital. Most of the practices had altered coverage schedule for the physicians. Strict protective measures during endoscopic procedures such as gowns, gloves, face shields, N95 masks, hairnets, double gloves, shoe covers, have also been implemented [87]. The patients are screened at arrival for symptoms and exposures. During the pandemic, only highly urgent endoscopic procedures are being performed on COVID-19 patients [88]. Endoscopy should be performed only when necessary and in a negative pressure flow room for COVID-19 patients if such a room is available. Where a negative pressure flow room for COVID-19 is not possible, strict sanitation measures are recommended [89].

Some of references need to be put in proper style..

- All references have been appropriately formatted into the National Library of Medicine (NLM) Style, including all authors and DOI, PMID, and PMCID.

(2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

- We have included original figure documents in the PowerPoint file to ensure that the editors can reprocess all graphs and arrows or texts portions.

(4) Please confirm if the figures are original.

- All our figures are originals.