

Dear Editor-in-Chief;

Thank you for your valuable review of our manuscript (62292, Review) entitled "**Review article: Gastrointestinal and hepatic diseases during COVID-19 pandemic; Manifestations, Mechanism and Management**". We have taken into consideration the referees' comments and made the suggested changes as possible. These revisions are summarized below:

Reviewer 1

Minor

- In these parts, I think the demographics of COVID-19 is not unnecessary because the authors described the demographics of Gastrointestinal and hepatic diseases in Table 1.

Answer:

First, thanks for your comment and we removed it as recommended.

- Then, the authors discuss the relationship between Gastrointestinal and COVID-19 in a lot of space with good figures. I suggest the authors add more contents related to liver function damage (which is very important) and how to evaluate the liver damage during COVID-19?

Answer:

We appreciate the reviewer's observation. The recommended data were added to the manuscript. (*Line 436-477, page 25-27*)

In addition, liver-associated clinical features as facial blackness and dull skin after COVID-19 recovery were added to the manuscript and it is illustrated with a figure in the manuscript (Figure 3). (*Line 510-530, page 30-32*)

- What are the pathological changes of hepatocyte under the damage of COVID-19?

Answer:

Thanks for your comment. The pathological changes of hepatocyte during COVID-19 damage were added as recommended. (*Line 482-501, page 28-29*)

- Is there any pathological picture?

Answer:

Unfortunately, we were unable to obtain permission to use hepatic pathological figures, but we have added additional satisfactory pathological data in our manuscript. (*Line 482-501, page 28-29*)

Reviewer 2

Minor

• Dear authors, Thank you for your submitting the manuscript entitled, "Gastrointestinal and hepatic diseases during COVID-19 pandemic; Manifestations, Mechanism and Management " to WJG. The manuscript is well written and compactly summarized, and the topic is interesting and timely. The manuscript is readable and the schematic figures are nice. References are very recently published or reported. I think it is almost OK as it stands. However one minor criticisms should be addressed as following. Minor 1. Please revise the whole manuscript following the WJG style.

Answer: Thank you for your comment and complete the modification.

Reviewer 3

Minor

- The authors need to add pathological findings of liver injury in the manuscript like steatosis and lobular activity. The authors need to added few articles on pathology also.

Answer:

Thanks a lot for this comment. The pathological findings of liver injury during COVID-19 were added as recommended. (*Line 482-501, page 28-29*)

As well, the microscopic changes of the GI tract were also added. (*Line 156-162, page 10*)

- Also rarely allograft injury is also described. Kindly add that also

Answer:

The authors were grateful for your comment. We added the recommended data to the manuscript. (*Line 646-670, page 37- 38*)

Reviewer 4

Minor

- Abstract: Written well. Please replace side effects with adverse events.

Answer: We are grateful for the reviewer's comment. We replaced side effects with adverse events as recommended. *(Line 30, page 2)*

- Images on page 3, well depicted. However change colon to GUT/ intestine (Colon is the main the organ involved in GI effects of COVID-19).

Answer:

Thanks a lot for the reviewer's effort. The colon has been replaced with GUT as recommended. *(Line 39, page 3)*

- Introduction: Start the introduction with coronavirus, prior outbreaks and current pandemic (PMID: 33282890 and PMID: 32281689).

Answer:

We appreciate the reviewer's comment. The recommended data were added. *(Line 51-59, page 5)*

- Provide 1-2 lines on the epidemiological data using Worldometer (use updated once).

Answer:

Thanks for your comment. The recommended data were added to manuscript. *(Line 61-62, page 5)*

- This should be followed by pulmonary and extrapulmonary manifestations of the COVID-19 (PMID: 32281689, PMID: 32903492, PMID: 32807535, PMID: 33349441, PMID: 33129845).

Answer:

Thanks for your comment. The recommended data were added to manuscript and it is illustrated with a figure (Figure 1). *(Line 65-80, page 5-6)*

- Provide data on race and gender changes (PMID: 32850607).

Answer:

The authors were grateful for your comment. The recommended data were added to manuscript *(Line 97-112, page 7-8)*

- Section on diagnosis of COVID-19 can be removed as this is unrelated to current manuscript GI manifestations:

Answer:

Thanks for your comment. This section was removed as recommended.

- Authors made good effort in describing the symptoms of GI effects. However they need to elaborate further on other GI effects such as a pancreatitis (PMID: 33129845), GI bleeding (PMID: 32516204), abdominal pain (PMID: 33330546).

Answer:

The authors were grateful for your comment. Indeed, the recommended data were added to manuscript. *(Line 125-155, page 8-10)*

- Page 9, last paragraph should be at the end.

Answer:

It is really a valuable point, so we allocated a separate section to "COVID-19 and the fecal-oral transmission route" after the "COVID-19 and pre-existing digestive diseases" section inside the manuscript. *(Line 362-380, page 22-23)*

- Mechanisms of GI injury: Authors discussion on the direct cytopathic effect, gut lung axis, drug effects. In the drug effects add the discussion on the PPI as these are commonly used in COVID with GI symptoms (PMID: 33252418).

Answer:

We appreciate the reviewer's observation and we added the recommended data to the manuscript. (*Line 276-294, page 17*)

- Furthermore, authors should mention that the true prevalence of GI symptoms are unclear due to studies evaluating the prevalence (with ruling out of the other causes are unclear and are likely overestimated) (PMID: 32535231).

Answer:

Thanks a lot for this comment. It was added to the "*Gastrointestinal Symptoms Caused by Drug Side Effects*" section as recommended. (*Line 271-275, page 16*)

- COVID and liver manifestations: This has been discussed extensively. Please add outcomes of the patients with severe elevation of aminotransferases in COVID-19 (refer to PMID: 32837096).

Answer:

The authors were grateful for your comment. We added the recommended data to the manuscript. (*Line 502-509, page 29- 30*)

- Endoscopy and COVID: First mention about the prior data on the duodenoscopy related infections (PMID: 30569333).

Answer:

Firstly, the authors were grateful for your comment. We added the recommended data to the manuscript. (*Line 720-737, page 42- 43*)

- Authors should add the splash rate in endoscopy units (PMID: 30391253, PMID: 31635718).

Answer:

It was added as recommended. (*Line 711-719, page 42*)

- Minimizing personnel and unnecessary instrumentation (PMID: 33330546, PMID: 33063878).

Answer:

The recommended data were added. (*Line 738-753, page 43- 44*)

- Further techniques to reduce splashes (PMID: 31635718) should be given.

Answer:

The recommended techniques were added. (*Line 753-755, page 44*)

- Mention gaps in the knowledge (though there is theoretical risk of feco-oral transmission, the actual risk of transmission is extremely low). Despite the risk, endoscopy units have been functioning and reopening with no significant outbreaks noted

Answer:

The authors were grateful for your comment. We added the recommended data to the manuscript. (*Line 756-759, page 44*)

