

ROUND 1

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

Specific Comments to Authors: Manuscript Number: 62256 Title: Acute Pancreatitis and COVID-19: a Literature Review The authors summarize the current knowledge on mechanisms of pancreatic injury by SARS-CoV2 and conducted a review of all published cases of AP in COVID-19 patients. The authors aim to clarify the relation between the ongoing pandemic and AP cases. Faced with the severe development trend of coronavirus disease 2019 pneumonia in the world, it is indeed necessary for us to deeply study various complications caused by COVID-19 in infected patients. The authors pay timely attention to the possible effects of COVID-19 on acute pancreatitis, as well as aspects that need to be considered in the management of infected patients. However, the authors conclude that there is currently insufficient evidence to suggest that COVID-19 causes acute pancreatitis or negatively affects prognosis. If it is the case, should the authors also study or focus on **other related pancreatic diseases**, such as diabetes, chronic pancreatitis, pancreatic cyst? For example, after the patient is cured of the virus infection, whether the patient will appear **pancreas-related sequelae**, such as diabetes, chronic pancreatitis, pancreatic cyst ? Overall, I think this is an interesting study with positive implications for the treatment of clinical COVID-19-related diseases. The manuscript can be accepted and published in World Journal of Gastrointestinal Surgery after major revision.

We thank the reviewer for the careful reading of our manuscript. Although there may be a plausible relation, there is still insufficient evidence to state that SARS-CoV-2 infection can cause or negatively affect prognosis of acute pancreatitis. Furthermore, the available evidence relies mostly on case reports and small case series, with short follow-up periods.

As we state in our review, Wang and colleagues, in a retrospective analysis indicated that 6 out of 9 patients with COVID-19 pneumonia and pancreatic injury developed blood glucose abnormalities and Gadiparthi and colleagues reported an AP case with new-onset type 2 diabetes. To our knowledge, no other pancreas-related sequelae are reported in the literature, and the patients' follow-up period is too short for chronic pancreatitis manifestations, namely imaging, to develop. We acknowledge the reviewer's comment and we added a remark on pancreas-related sequela on the discussion and conclusion (highlighted in pink).

There is a need for solid population-based epidemiological studies and carefully designed cohort studies to carefully assess the incidence of acute pancreatitis in both the COVID-19 and the pre-COVID-19 era and the clinical progression of these patients. Furthermore, patients with suspected SARS-CoV-2 induced acute pancreatitis should be followed in time to assess patient's recovery and/or associated complications, including new-onset diabetes, pancreatic exocrine insufficiency, pancreatitis induced local complications, namely pseudocysts, and/or chronic pancreatitis.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The authors present a manuscript overlooking correlations of acute pancreatitis with new coronavirus infection and literature available on the matter. Overall, it is a good article, well structured and easy to read. Mechanism of potential impact of coronavirus on pancreatic cells are described in detail, however, a **schematic figure** depicting these mechanisms would be welcome; please consider the latter and add it to the manuscript. Analysis of available case reports has been thorough and they have critically evaluated the results. It is good that no conclusions in favor of direct connection with AP have been drawn as no such correlations have been proven thus far.

We thank the reviewer for the careful reading of our manuscript and for the comments. We have included in the manuscript a schematic figure depicting the pathophysiology of SARS-CoV-2 injury to pancreatic cells, according these comments (changes in the text highlighted in yellow)

Reviewer #3:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: 1.Minor comment,"SARS-CoV2"should be "**SARS-CoV-2**". 2.Authors conducted an in-depth analysis on the mechanisms of pancreatic injury by SARS-CoV-2 and reviewed published cases of AP in COVID-19 patients. Please state the **treatment of AP in COVID-19 patients**. 3.Please state the **prognosis of patients with AP in COVID-19**.

We thank the reviewer for the careful reading of our manuscript and for the suggestions.

1. We agree with the reviewer remark and changed the term throughout the manuscript (term replacement signaled in red).
2. Most evidence on acute pancreatitis cases in COVID-19 patients rely on small case series and case reports and there are no management guidelines specific for this subset of patients. As such, in our review, we cannot make any recommendations on the treatment of this specific group of patients that aren't already considered in international guidelines for the treatment of patients with acute pancreatitis. General supportive measures and aggressive fluid resuscitation guided by the patient's hemodynamic status should be the mainstay of treatment. Drugs known to be associated with pancreatic lesion should also be omitted when possible. However, this decision should be made individually, as many drugs used in the COVID-19 treatment algorithm may be associated with pancreatitis. We added a paragraph in the discussion relating to the treatment of these patients (highlighted in light blue).
3. There are few cohort studies on pancreatic lesion/pancreatitis in COVID-19 patients and published case reports and case series have very short follow-up periods. Acute pancreatitis severity is also not always assessed and stated in published case reports which renders it even more difficult to explore the possible relation between disease severity and COVID-19 severity. As such, no considerations on the prognosis of AP in COVID-19 can be made. We acknowledge the reviewer's comment and added a small consideration on the prognosis of these patients (highlighted in red)

More robust data and national and international registries are needed to better understand and clarify the conundrum of SARS-CoV-2 infection and associated pancreatic injury/pancreatitis, before any recommendations on the treatment of these patients can be made.

Reviewer #4:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This manuscript has reviewed acute pancreatitis by COVID-19. This issue is important and interesting. However, it will require some revision before publication. 1, Both severe acute pancreatitis and COVID-19 infection often show a cytokine storm, and COVID-19 may affect the severity of acute pancreatitis. However, how do the authors **differentiate** severe acute pancreatitis caused by COVID-19 from severe acute pancreatitis with COVID-19?

We thank the reviewer for the careful reading of our manuscript and for the interesting question. In fact, both severe cases of acute pancreatitis and COVID-19 are characterized by a cytokine storm, as we refer in our manuscript. Furthermore, similar patterns of cytokine elevation between the two entities have been found.

We acknowledge the reviewer's comment and modified the paragraph on cytokine storm and in the conclusion (changes highlighted in **green**). At this point, it is not possible to distinguish what generated the cytokine storm in cases where severe acute pancreatitis coexist with COVID-19, besides a possible temporal relation. Prediction of disease course, assessment of disease severity in the background of COVID-19 and overall outcome when these two entities coexist are some of the most pertinent open research questions. Further studies are needed to directly exploit a causal relationship between SARS-CoV-2 and acute pancreatitis.

(1) Science editor:

1 Scientific quality: The manuscript describes a systematic review of the acute pancreatitis and COVID-19. **The topic is within the scope of the WJGS.**

(1) Classification: Grade B, Grade C, Grade C and Grade D;

(2) Summary of the Peer-Review Report: Overall, it is a good article, well-structured and easy to read. Mechanism of potential impact of coronavirus on pancreatic cells are described in detail. **Please state the prognosis of patients with AP in COVID-19.** The **questions raised by the reviewers** should be answered; and

(3) Format: There are 4 tables and 4 figures. A total of 42 references are cited, including 33 references published in the 2020. There are no self-citations.

We thank the Editor for the careful reading of our manuscript and acknowledge the comments. Due to the paucity of literature, patient short follow-up periods and some contradicting observations, at this point there is insufficient evidence to state that COVID-19 can negatively impact AP prognosis. Further well designed studies with longer follow-up periods of acute pancreatitis cases in COVID-19 patients are needed to clarify this subject.

The questions raised by the reviewers were individually considered and answered. Appropriate modifications were made to the manuscript and highlighted.

2 Language evaluation: Classification: Grade A, Grade B, Grade B and Grade B.

3 Academic norms and rules: The authors need to provide the **Biostatistics Review Certificate**, the **signed Conflict-of-Interest Disclosure Form** and **Copyright License Agreement**, and the **PRISMA checklist**. No academic misconduct was found in the Bing search.

4 Supplementary comments: This is an invited manuscript. The topic has not previously been published in the WJGS. The corresponding author has not published articles in the BPG.

5 Issues raised:

(1) I found no **“Author contribution”** section. Please provide the author contributions;

We acknowledge the Editor’s comment and an “Author contribution section was added on the title page, accordingly.

(2) I found the authors did not add the **PMID and DOI in the reference list**. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

We acknowledge the Editor’s comment and the reference list was reviewed accordingly.

(3) I found the authors did not write the “article highlight” section. Please write the **“article highlights”** section at the end of the main text;

We acknowledge the Editor's comment and an "Article Highlights" section was added at the end of the main text, accordingly.

(4) I have changed the manuscript type "review" to "systematic review". Please revise the manuscript according to the Guidelines and Requirements for "**systematic review**"; and

We thank the Editor for the careful reading of our manuscript and for having changed the manuscript type to "systematic review". A review was made to fulfill the guidelines and requirements for a systematic review.

(5) the author should number the references in Arabic numerals according to the citation order in the text. The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author's name, with no spaces.

We acknowledge the Editor's comments and a careful review of all references was made to fulfill the requirements.

6 Re-Review: Required.

7 Recommendation: Conditionally accepted.

Company editor-in-chief

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Surgery, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

ROUND 2

We thank the Editor for the careful review of our manuscript and apologize for not having successfully marked the changes made in our review. We attach the manuscript with the requested marks and highlights.