

Peer Review File

Article information: <https://dx.doi.org/10.21037/tgh-23-58>

Reviewer A

1.mortality - while this is likely in-hospital/30-day mortality, please specify as they are not interchangeable.

Response : Thanks for your thoughtful suggestion. For mortality statistics in the included studies, in-hospital mortality was clearly indicated in Miró and Samanta, 30-day mortality was clearly indicated in Pandanaboyana, while other studies did not specify and only said "mortality". Therefore, our study focused on reporting mortality without making obvious comparisons. These factors may have influenced outcomes, as we have noted in our discussion.

Changes in the text: we have modified our text as advised (see Page 10, line 4-9)

2.definition of severe pancreatitis - the authors used BISAP score of 3 or more to define severe pancreatitis. is there any reason for this definition? severity stratification for AP is not classically defined using BISAP, the atlanta classification is more commonly used to define severe AP, while other scoring systems predict mortality/severity of AP but does not imply that there is severe AP. please cite PMID: 36504520

> also, as the authors specifically mentioned BISAP 3 or more was used to define severe AP, does this mean that all included studies in the meta-analysis for severe AP (Fig 5) used BISAP score?

Response: Thanks for your positive comment on the present study and insightful suggestion. In the study by Gompertz (PMID: 23282769), BISAP score > 3 has a good correlation with the development of local complications and organ failure. Although we generally use the Atlanta classification to classify the severity of acute pancreatitis, I use the BISAP score because there are few studies available and all five studies included in my meta-analysis of severe pancreatitis used the BISAP score.

Changes in the text: We have added some references to aid in the text (see Page 13, line 32-34)

3.One important question would be - whether it was covid-19 with concomitant AP which resulted in disease severity and mortality, or was it covid-19 induced AP which resulted in disease severity and mortality.

- the authors did a meta-analysis for the etiology of idiopathic AP and showed that COVID-19 + AP had more idiopathic AP. may i ask what is the definition of idiopathic AP - i.e. what is the extent of investigations performed before determining that the etiology of AP was idiopathic?

- literature on COVID-19 as a cause of AP is rare - there is a good summary on case

reports of covid-19 induced AP which deserves citation - about 70 so far in literature.
Cite PMID: 37155526

Response: Thank you for your insightful suggestion. Regarding whether COVID-19 is the cause of AP, unfortunately, due to the small number of existing clinical studies, this meta-analysis cannot strongly explain the causal relationship between the two. The results in this paper show that COVID-19 + AP has more idiopathic AP, which is also our effort to explore the causal relationship. For idiopathic AP, it was not clearly defined in the five studies we included, but common causes such as alcohol, gallstones, and hyperlipidemia type were excluded in each study. We also contacted the authors to seek a definition of idiopathic but were unable to obtain results. Therefore, after excluding some known causes of AP, we combined idiopathic AP with unknown causes for the analysis of results.

Changes in the text: we have modified our text as advised (see Page 9, line 11-17)

4. Results wise, I believe most studies are retrospective in nature (authors also did not mention this)

- please include nature of study, retrospective vs prospective

Response: Thank you for your correction. I have revised my text as suggested.

Changes in the text: we have modified our text as advised (see Page 10, line 3-4)

5. There is a lack of patient demographics which limit the interpretation of results. patients with covid-19 may have worse outcomes due to age, underlying co-morbidities. need for icu admission may be due to covid-19 in a high risk patient rather than AP. please include patient demographics + meta-analysis comparing patient demographics between covid-19 and no covid-19

Response: Your comments are very valuable. But in the studies included in this meta-analysis, the demographic composition of the age groups analyzed is very similar, and no meaningful information on this topic can be inferred. See Table 1 for the detailed population age. We also contacted the authors in an attempt to obtain specific information, but were not able to obtain all raw data. At the same time, we also searched the relevant literature to try to address this issue, but the current study seems to be consistent with ours (PMID: 37475841). High-risk patients who required icu admission probably had COVID-19 rather than AP - unfortunately, our study included only patients with and without AP. Therefore, we could not explore whether COVID-19 was an independent risk factor for ICU admission. It is expected that more studies will compare the treatment of COVID-19 patients with and without AP, so as to better prove the independent effect of COVID-19. We also have a discussion on this issue.

Changes in the text: we have added some discussion as advised (see Page 10, line 10-19).

6. One major area that is lacking is the discussion. The authors did discuss about the pathophysiology of covid-19 in ap, and other possible etiologies of ap in covid-19, such as medication use. However, there was no discussion on the results of the study. The authors need to discuss the following

- where this study should be covid-19 induced AP, or covid-19 + concomitant AP, and state the difficulty in establishing etiology as above mentioned

Response: The results of this study can only prove that SARS-CoV-2 is a risk factor for poor outcome in acute pancreatitis, rather than a cause of acute pancreatitis. Most of the studies included in this article are retrospective studies, and the studies we can include are quite limited due to the small number of relevant clinical studies. Therefore, we hope that more prospective, multicenter studies can better explore the causal relationship between COVID-19 and AP, and play a certain guiding role in clinical work.

Changes in the text: we have added some discussion as advised (see Page 11, line 19-21).

- while worse outcomes are noted for covid-19 AP, this is likely confounded by multiple reasons e.g. patient demographics (which authors need to show in the results)

Response: Thank you for your correction. I have added a discussion to the text.

Changes in the text: we have added some discussion as advised (see Page 10, line 20-28; Page 11, line 1-13).

- whether treatment was received for covid-19 e.g. paxlovid and how this impacts outcomes

Response: Treatments for COVID-19 were not described in the included studies, so their effect on outcomes is unknown. We added a discussion in the text.

Changes in the text: we have added some discussion as advised (see Page 10, line 20-22).

- is there any subgroup analysis for non idiopathic pancreatitis e.g. gallstone pancreatitis, and how will this affect the outcomes?

Response: Because some of the included articles did not specify the type and the number of patients with idiopathic pancreatitis, this article only analyzed idiopathic pancreatitis, and no subgroup analysis was performed on non-idiopathic pancreatitis, so the effect of non-idiopathic pancreatitis on the outcome cannot be discussed. We hope that more clinical studies can further explore its effect on the outcome in the future.

Reviewer B

1. In the section of Abstract, Discussion should be amended. It is not appropriate to include the limitations of your research only. It is better to list the main points of this meta-analysis.

Response : Thanks for your careful attitude. I have removed the discussion section of the abstract, as requested in the journal's author's guide, but have added the highlights of this meta-analysis to the discussion section of the main text.

Changes in the text: we have added some discussion as advised (see Page 2, line 19-21/Page 9, line 1-30/Page 10, line 1-2).

2. In Page4, line 23, ULN should display its full name “Upper Limit of Normal”, or you

can add an abbreviation table that includes ULN, AP, etc.

Response : Thank you for your correction. I have revised my text as suggested.

Changes in the text: we have modified our text as advised (see Page 5, line 3)

3. There was obvious heterogeneity ($I^2 > 50\%$) in ICU admission, mechanical ventilation, and severe pancreatitis. In addition to random effects model, did you use other methods, such as subgroup analysis, to reduce the impact of heterogeneity?

Response : Thank you for your valuable suggestions. There is obvious heterogeneity in the above three studies, so I conducted sensitivity analysis to reduce the impact of heterogeneity. See page 7, line 4-6/13-15/24-25 for details.

4. In Page 9, the section of Conclusion, you mentioned that “we speculate that SARS-CoV-2 may be an important cause of acute pancreatitis”. However, in your article, your results prove that SARS-CoV-2 is a risk factor for poor outcomes of acute pancreatitis instead of a cause of acute pancreatitis. So, this sentence may not be appropriate.

Response : Thank you for your correction. I have revised my text as suggested.

Changes in the text: we have modified our text as advised (see Page 12, line 27-29)

5. The language of this meta-analysis should be modified and polished.

Response : Thanks for your suggestion, it is very important for the quality of our manuscript. We have invited experts for English writing to help us with proof reading for English language. We hope that the revised manuscript will meet with approval. If you still suggest us to modify the language later, we will modify it again.

6. There are several guidelines about the therapy of acute pancreatitis. Can you briefly introduce the treatment of COVID-19 patients with acute pancreatitis in the section of Discussion? The following is a guideline to the treatment of acute pancreatitis. Please include this reference into your article.

New guidelines for the treatment of severe acute pancreatitis. (doi: 10.21037/hbsn-22-532)

Response : Thank you for your suggestion, but at present, there is no relevant guideline for COVID-19 complicated with acute pancreatitis that clearly points out the treatment method. Some case reports of acute pancreatitis caused by COVID-19 are also symptomatic treatment for different clinical symptoms of patients. We are looking forward to the writing of relevant guidelines by authoritative experts. To guide clinical treatment. I have revised it as suggested and included the references in the article

Changes in the text: we have modified our text as advised (see Page 15, line 30-31)