

December 25, 2019

Dear Editor:

Thank you very much for giving us the opportunity to further revise our paper. Please contact me if there are any questions. I'd like to revise the paper according to your advise. Please find enclosed the edited manuscript in Word format (file name: 53074-revised manuscript file. docx).

**Title: The severity of acute gastrointestinal injury grade is a good predictor of mortality in critically ill patients with acute pancreatitis**

**Author:** Ling Ding, Hong-Yan Chen, Jing-Yun Wang, Hui-Fang Xiong, Wen-Hua He, Liang Xia, Nong-Hua Lu, Yin Zhu

**Name of Journal:** World Journal of Gastroenterology

**Manuscript NO:** 53074

The manuscript has been improved according to the suggestions of the editor and the reviewers:

1 Format has been updated

2 Revisions have been made according to the suggestions of the editors and reviewers

**Reviewer 1**

**The manuscript is well researched and written. However, I have a few queries.**

*Comment 1: The commonest cause for AP was hyperlipidemia? How was this*

*diagnosis made? If this is true, these results may not be generalised to other populations. This should be mentioned in the limitations.*

Response: Thank you for this valuable comment. The diagnosis of hyperlipidemia pancreatitis is made when a serum triglyceride is greater than 1000 mg/dL or a serum triglyceride is between 500 mg/dL and 1000 mg/dL combined with chyle-like serum and exclusion of biliary pancreatitis and alcoholic pancreatitis. There are several reasons for the high rate of hyperlipidemia pancreatitis. Firstly, the diagnosis of hyperlipidemia pancreatitis is more broad, which might account for the high rate of hyperlipidemia pancreatitis. Secondly, hyperlipidemia pancreatitis is reported to be more common in Chinese people, and is considered to be the second etiology of acute pancreatitis.<sup>[1,2]</sup> Thirdly, high serum TG level is related to poor outcome and especially in the acute stage of pancreatitis, may lead to the organ failure and ICU stay.<sup>[1,2]</sup> As we included patients with AP admitted to our pancreatic intensive care unit, we may included more patients of hyperlipidemia pancreatitis. As this were a single-center study, it may limit the representativeness, and this was mentioned in the limitations in the revised revision.

1 **Zhu Y**, Pan X, Zeng H, He W, Xia L, Liu P, Zhu Y, Chen Y, Lv N. A Study on the Etiology, Severity, and Mortality of 3260 Patients With Acute Pancreatitis According to the Revised Atlanta Classification in Jiangxi, China Over an 8-Year Period. *Pancreas* 2017; 46: 504-509 [PMID: 28196012 DOI: 10.1097/MPA.0000000000000776]

[2] **Zheng Y**, Zhou Z, Li H, Li J, Li A, Ma B, Zhang T, Liao Q, Ye Y, Zhang Z, Yang Y, Wang Z, Zhang Z, Yang J, Li F. A multicenter study on etiology of acute pancreatitis in Beijing during 5 years. *Pancreas* 2015; 44: 409-414 [PMID: 25438072 DOI: 10.1097/MPA.0000000000000273]

*Comment 2: How was the diagnosis of infective necrosis made?*

Response: Thank you for this valuable comment. The diagnosis of infective necrosis was confirmed by a positive or fungal culture or Gram stain of pancreatic or extrapancreatic necrosis obtained by fine needle aspiration or from the first drainage procedure or the first necrosectomy according to the definition of 2012 Atlanta Classification, which was named as “infected pancreatic necrosis”.

## **Reviewer 2**

**A very valuable study that compares traditional scales for a simpler predictive and feasible tool.**

Response: Thank you for your review. We hope that this study will help.

## **Reviewer 3**

**In this retrospective study, Ding et al. incorporate acute gastrointestinal injury (AGI) grade to predict the mortality of severe acute pancreatitis. It showed AGI scores III/IV were associated with a significantly higher mortality rate in ICU acute severe pancreatitis patients.**

*Comments 1: The percentage of hypertriglyceridemia related to acute pancreatitis is much higher than in other studies (line 112). Do authors have etiologies of hypertriglyceridemia (medication, poor control DM, alcohol use, familial hypertriglyceridemia) and more detail levels of serum triglyceride (TG)? In our experience, high serum TG level is related to poor outcome and in the acute stage of pancreatitis, and prolonged high level of TG might be related to prolonged feeding intolerance. The author may need to check if hypertriglyceridemia is a confounder or effect modifier. (Ex. By performing chi2 squared test stratified by hypertriglyceridemia, we can know whether hypertriglyceridemia is a confounding factor for AGI and mortality. If the*

*odds changes a lot from the original odds, crude odds, hypertriglyceridemia may be confounder or effect modifier.) If hypertriglyceridemia is a confounding factor or effect modifier, the author needs to mention it in the discussion.*

Response: Thank you very much for your valuable comment. The diagnosis of hyperlipidemia pancreatitis is made when a serum triglyceride is greater than 1000 mg/dL or a serum triglyceride is between 500 mg/dL and 1000 mg/dL combined with chyle-like serum and exclusion of biliary pancreatitis and alcoholic pancreatitis. The diagnosis of hyperlipidemia pancreatitis is mostly depended on the level of serum triglyceride within 48h of acute pancreatitis onset. As we are a tertiary referral hospital, the diagnosis of hyperlipidemia pancreatitis is mostly depend on the serum triglyceride level tested at other hospital. As this were a retrospective study, we apologized that we did not have more details of etiologies of hypertriglyceridemia (medication, poor control DM, alcohol use, familial hypertriglyceridemia) and more detail levels of serum triglyceride (TG), especially at onset of acute pancreatitis. We considered hypertriglyceridemia as a possible cofounder factor. In the univariate logistic regression analysis, we included etiology as a possible cofounder factor, which included hypertriglyceridemia pancreatitis. However, we found the etiology was not significantly associated with mortality. As we did not have more detail levels of serum triglyceride, we could not further analysis the relationship between the level of hypertriglyceridemia and mortality, and we considered this was a limitation.

*Comment 2: In AGI grade III (n=93), how many patients underwent nasojejunal (NJ) feeding? Are there any difference in outcomes of infections and mortality between patients with/without NJ feeding? This can be mentioned in the result and discussion.*

Response: Thank you very much for your valuable comment. The AGI grade

was assessed according to the recommendation of the ESICM during the first week of the subject's ICU stay. This system is mainly based on GI symptoms and IAP on days 1-3 of ICU admission, and it is concomitantly combined with feeding intolerance (FI) on the remaining 4 days. The global AGI grade was determined on the basis of the worst AGI grade within the first week of ICU admission. In AGI grade III (n=93), all patients underwent nasojejunal (NJ) feeding. Enteral nutrition was initiated according to current clinical practice guidelines for nutritional support in AP patients<sup>[错误:未找到引用源。 4]</sup>. FI should be considered present if at least 20 kcal/kg BW/day via enteral route cannot be achieved within 72 h of a feeding attempt or if enteral feeding has to be stopped for any clinical reason. As we included all patients admitted to our pancreatic intensive care unit, and all patients underwent nasojejunal (NJ) feeding, it was impossible to find out any difference in outcomes of infections and mortality between patients with/without NJ feeding.

3 **Crockett SD**, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN; American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. *Gastroenterology* 2018; 154: 1096-1101 [PMID: 29409760 DOI: 10.1053/j.gastro.2018.01.032]

4 **Tenner S**, Baillie J, DeWitt J, Vege SS; American College of Gastroenterology. American College of Gastroenterology Guidelines: Management of Acute Pancreatitis. *Am J Gastroenterol* 2013; 108: 1400-15;1416 [PMID: 23896955 DOI: 10.1038/ajg.2013.218]

*Comment 3: In the final paragraph, the first statement can be more specific rather than the statement "In conclusion, the AGI grade is useful for assessing the severity of GI dysfunction and could be used as a predictor of mortality in critically ill patients with AP."*

Response: Thank you for your comment. I change the statement into "In

conclusion, the AGI grade is independent predictor for mortality in critically ill patients with AP. The AGI grade combined with the APACHE II, Modified Marshall, and Ranson scores allows better prediction of mortality than does the use of any of these scoring systems alone” in the revised revision.

#### **Reviewer 4**

This is an interesting manuscript about the association between acute gastrointestinal injury (AGI) grade and clinical outcomes in critically ill patients with acute pancreatitis. The data demonstrated that the AGI grade was more useful for predicting mortality. This manuscript is nicely structured and well written. However, I have a few minor comments about this manuscript. Please consider the following comments.

*Comment 1: All through the manuscript (include Table) The authors should correct “p =0.000” to “p <0.001”.*

Response: Thank you for your comment. I apologize for my mistake. I revised this.

*Comment 2: Figure 1 I think “Exclusion” or “Exclude” should be substituted for “Inclusion”.*

Response: Thank you for your comment. I apologize for my mistake. I revised this.

#### **Reviewer 5**

The manuscript studies the relationship between GI dysfunction and outcomes of AP among those hospitalized to the ICU. The analyses includes a multivariate analysis showing independent association with mortality. Other than the fact that this is a retrospective study, the manuscript is well

**written, analyses are adequate, and the conclusions drawn are appropriate. I do not see any major methodological issues in the manuscript.**

Response: Thank you for your review. We hope that this study will help.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely,

Yin Zhu, PhD, professor

Department of Gastroenterology

The First Affiliated Hospital of Nanchang University

17 YongWaizheng Street, Nanchang, 330006, Jiangxi Province, China

Telephone: +86-791-88692540 Fax: +8679186292217

E-mail: zhuyin27@sina.com