

August 5, 2019

To: Ya-Juan Ma, Science Editor, World Journal of Hepatology
Li Ma, Editor-in-Chief, World Journal of Hepatology
From: David Snell, Arun Jesudian
Subject: Response to comments for manuscript 48517

Dear Dr. Ma,

We greatly appreciate the comments from the reviewer and editorial staff. We believe the changes made to our paper, "Gastric Food Retention at Endoscopy is Predicted by Severity of Liver Cirrhosis," have significantly improved the strength of the manuscript. We have italicized the changes in the revised manuscript. Please see our point-by-point reviewer responses below:

Reviewer 03488192:

Title.- Although the statistical tests show there is a significant OR for food retention assuming that the DGE is a valid test for studying gastric emptying with a reasonably high specificity there are some other factors like those associated with insulin resistance that were not studied but could be related as well because there is also a significant association with diabetes (table 3). The Child-Pugh classification includes several parameters that have been studied as factors associated with gastric retention and it is difficult to demonstrate associations with each individual factor or resulting in mixed results as expressed by the authors. For those reasons I suggest that the title should read "Gastric Food Retention at Endoscopy is associated with the Severity of Liver Cirrhosis"

We have changed the title of our study to "Gastric Food Retention at Endoscopy is Associated with Severity of Liver Cirrhosis" in order to more accurately reflect the scope of our study. There are several pathophysiologic mechanisms that are thought to lead to delayed gastric emptying, including insulin resistance. While our study did make note of the significant association with diabetes, we did not specifically examine gut hormonal alterations. Additionally, given that the prior literature regarding the association between Child-Pugh class and delayed gastric emptying is mixed, we felt the phrase "predicted by" reflected a level of surety not yet established in the existing literature.

Results.- Authors do not report the presence of pyloric stenosis, which should have been included in the EGD report, and should mention whether it was reported in all the cases included.



The presence of pyloric stenosis was part of the data gathered as part of the endoscopic findings. To clarify this point, we have added “presence of pyloric stenosis or other evidence of gastric outlet obstruction” to the description of endoscopic information collected in the Materials and Methods section. Upon our review of the endoscopic reports, there were no endoscopies in the case or control group that had the presence of pyloric stenosis or other causes of gastric outlet obstruction. Thus, in the Results section we included the sentence “No patients had evidence of pyloric stenosis or other causes of gastric outlet obstruction on endoscopy.”

Discussion.-The authors have cited most of the important previous studies on delayed gastric emptying (DGE) in cirrhotic patients. In reference No. 17, Kalaitzakis et al. report that DGE is associated with insulin resistance which is characterized by hyperglycemia, hyperinsulinemia and hypoghrelinemia. It is noteworthy that the authors do not mention that in the discussion when it could be suspected that their results could agree or support that conclusion. In another of the references cited, No. 13, Chang et al. reports that DGE is associated with patients degree of Child Pugh’s classification with higher prevalence in patients with Child-P C degree. The results with different type of analysis are in the same direction and that should be part of the discussion. From the list of references and some other not included like Kao et al. (Nuclear Medicine 1996), Kaohslung et al. (J Med Sci 1996) it is clear that the phrase “...one of the first studies to investigate risk factors ...” in the first line 3rd paragraph of the discussion should be excluded.

Our data lends support to the role of insulin resistance in the pathogenesis of delayed gastric emptying in patients with cirrhosis. As the reviewer notes, Kalaitzakis et al, among others, has reported this previously. In order to emphasize this, in the second paragraph of the discussion section, we added the sentence, “Gut hormonal alterations related to insulin resistance, including hyperglycemia, hyperinsulinemia, and hypoghrelinemia can play a prominent role in the pathophysiology of delayed gastric emptying in patients with cirrhosis^[17].” Additionally, we added the following sentence in the third paragraph of the discussion section in order to expound upon the importance of our results: “The association of diabetes with delayed gastric emptying lends further support to the role of insulin resistance in the pathogenesis of gastroparesis in cirrhotic patients, as previously described in Kalaitzakis et al^[17].”

Chang et al reported a trend towards significance with higher prevalence of delayed gastric emptying in patients with Child-Pugh C cirrhosis versus Child-Pugh A cirrhosis. However, this result was not statistically significant. Nonetheless, it is noteworthy that Miyajima et al and Gumurdulu et al both showed correlation between severity of Child-Pugh class and prevalence of delayed gastric emptying. Both used methodology different than that used in our study but with similar conclusions. In order to emphasize the importance of our results in the context of these prior studies, we have added the following to the third paragraph of the discussion section: “However, the correlation between severity of cirrhosis and delayed gastric emptying seen in this study is similar to two previous studies^[1,14]. Gumurdulu *et al* demonstrated that Child-Pugh class correlated with delayed gastric emptying, as measured by scintigraphy, and Miyajima *et al* concluded a similar association using measurements of autonomic function and portal blood flow *via* MRI^[1,14]. Despite the different methodologies used in



those studies and the present study, the similar conclusions lend further credence to the results of the current study.”

Given the number of prior studies investigating risk factors for delayed gastric emptying in cirrhosis, we deleted the first sentence of the 3rd paragraph of the discussion that read “This is one of the first studies to investigate risk factors for delayed gastric emptying in cirrhosis.”

Reviewer 00503773:

I read the manuscript named “ Gastric Food Retention at Endoscopy is Predicted by Severity of Liver Cirrhosis”. (Manuscript NO: 48517) and my recommendations are as fallows. Title: It is accurately reflects the major topic and contents of the study. Abstract: Adequate, summarizing the topic. Discussion: Topics has been discussed with all aspects. Tables are reflects the major findings of the study, and they are appropriately presented. References are appropriate, relevant, and updated. This manuscript was well-written and documented. I think that this manuscript is suitable and worth to be published in the World Journal of Hepatology.

Reviewer 00039368:

This is well designed, performed and written retrospective case-control study for the evaluation of relative frequency of delayed gastric emptying among patients with liver cirrhosis and identification of associated factors. The authors investigated a remarkable amount of persons: altogether 364 patients with confirmed cirrhosis and 519 controls patients without liver disease. The authors give a sufficiently clear overview about the study background and raised clearly the aim of the study, which is fulfilled. The statistical analysis was specified sufficiently well. The material studied is large enough and allows to drawn the conclusions. The Results are presented clearly. The paper is supplied with 3 Tables and one Figure which give very good overview about the results and are presented very clearly and correctly. The authors found that cirrhosis predispose to higher frequency of retained food at esophagogastroduodenoscopy. Additionally, decompensated cirrhosis, also age younger than 60, diabetes mellitus, use of opioids, thrombocytopenia considered to be associated with a higher probability of delayed gastric emptying. The following point need to be considered: 1. In Discussion it should more discussed and explained the result considered association of gastric retention with age younger than 60 years. How do you explain this fact?

In the general population, it is fairly well established that the incidence of gastroparesis increases with advanced age. In our cohort of cirrhotic patients, it is unclear why gastric food retention was associated with age younger than 60. Given that young age was associated on univariate analysis but not multivariate analysis, there are likely confounding factors. To reflect this, the following sentence was added to the third paragraph of the discussion section: “Regarding the association of age and gastroparesis, it is unclear why gastric food retention was associated with younger age. Given that



young age was associated with delayed gastric emptying on univariate analysis but not multivariate analysis, there are likely confounding factors at play.”

Reviewer 03262874:

This is a well written manuscript. The methods are good especially with eliminating the confounding factors. Although, it is intuitive, demonstrating that cirrhosis is associated with gastroparesis is good.

In response to the Editor’s comments:

- We have changed the title of our study in order to more accurately reflect the scope.
- We have clarified that the presence of pyloric stenosis was investigated and was not present in any of the case or control cases.
- We have expounded on the importance of our results with regard to supporting both insulin resistance and portal hypertension as important factors in the pathophysiology of delayed gastric emptying in patients with cirrhosis.
- We have commented on the association between delayed gastric emptying and younger age and determined this is most likely due to confounding factors.
- We have added a short running title.
- We have created an audio file for the audio core tip.
- We have added the “Article Highlights” section.
- We have listed all authors and available PMID and DOI information in the “References” section. All cited references have an associated PMID.
- We have edited Figure 1, including font and size, and have provided the PowerPoint format.

We hope that these changes have adequately addressed the reviewer commentary. Please let us know if you have any further questions regarding our submission.

Sincerely,

David Snell