ANSWERING REVIEWERS

January 31, 2022

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 74253_Auto_Edited.docx).

Title: Clinical manifestations and outcomes in gastric antral vascular ectasia (GAVE) according to endoscopic patterns and the presence of cirrhosis

Author: Hyo Jin Kwon, Si Hyung Lee, Joon Hyun

Name of Journal: *World Journal of Clinical Cases*

ESPS Manuscript NO: 74253

Thank you very much for your kind comments.
We tried to revise the manuscript as much as possible according to the suggestions made by the reviewers and the Editorial Office's comments and suggestions, and enclosed revision detail and revised manuscript.
We hope all these revisions will be satisfactory.

The manuscript has been improved according to the suggestions of reviewers and the Editorial Office's comments and suggestions:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Answers to Reviewer No. 05230210
(highlighted by yellow color in the updated version of the manuscript)
Notes on the manuscript:
• I would like to thank the authors for their manuscript. However, I think the (Title and aim) have been researched before and the results of the study do not offer a new view on the topic. The only new part is the long-term follow up data of the patients and I think what the authors should concentrate on in writing the title, aim and abstract. I suggest (Long term outcomes of different patterns of GAVE). Or concentrate on the geographical variability.

We really appreciate your valuable and delicate advice and suggestions. As your comment, the "Title" was changed and the "AIM" in the "Abstract" was carefully polished.

• There is no mention of the type of study is it cross sectional or case-control or cohort? Prospective or retrospective? (I think as you mentioned in the methodology of the manuscript it is a retrospective cohort)

Thanks for your delicate remark. We mentioned the type of study in the "*Study design and patients*" part of the "MATERIALS AND METHODS" section. (at the bottom of the page 4 of the revised manuscript)

• Why no histopathological biopsy of the GAVE was assessed? could the authors clarify.
The diagnosis of GAVE is mainly based on endoscopic pattern and, for uncertain cases, on histology.

Although it was unclear why the biopsy was not performed for the diagnosis of GAVE due to the retrospective nature of this study, we confirmed that there were no uncertain cases through careful reviews of endoscopic photo by three skilled gastroenterologists.
We understand your concerns. I have tried to describe as much as possible what you have pointed out in the "*Diagnosis and endoscopic classification*" part of the "MATERIALS AND METHODS" section. (at the page 5 of the revised manuscript)

• Watermelon stomach mostly means the stripped pattern, while punctate type is not. Another type of diffuse telangiectasia is called " honeycomb" appearance (references: Fuccio L, Mussetto A, Laterza L, Eusebi LH, Bazzoli F. Diagnosis and management of gastric antral vascular ectasia. World J Gastrointest Endosc. 2013 Jan 16;5(1):6-13. doi: 10.4253/wjge.v5.i1.6. PMID: 23330048; PMCID: PMC3547119.)

The terminology used in various literatures is slightly different. In order to avoid confusion, as your comment, the terms were finally described as follows; "punctate" (diffuse, honeycomb) / "striped" (linear, watermelon) in the "*Diagnosis and endoscopic classification*" part of the "MATERIALS AND METHODS" section. (at the bottom of the page 5 of the revised manuscript)

• The conclusion of this study was mentioned before, so I suggest considering concentrating on the long term outcome only, also the discussion will be enriched if the authors explained why their group of cirrhotic patients showed this favorable outcome similar or better than to the non-cirrhotic which is not common in clinical practice.

As your comment, we have tried to modify the "CONCLUSION" section of the text by focusing on the long-term outcome.
The difference of the clinical presentation such as GI bleeding in GAVE with LC or without could not be fully explained. As your comment, we added these carefully to the" DISCUSSION" section of the text. (at the page (bottom)11-(top)12 of the revised manuscript)

• The results section didn't mention the histology of the cirrhosis, although it is mentioned in the methodology that some of the patients were diagnosed by liver biopsy. Also, could the authors mention why the patients performed the biopsy in the first place, as it is not ethical as a routine measure.

In cirrhosis patients included in this study, liver cirrhosis was diagnosed clinically based on radiology and blood tests. We are very sorry to make you confuse. In the "*Study design and patients*" part of the "MATERIALS AND METHODS" section, the sentence about the diagnosis of liver cirrhosis has been corrected. (at the page 5 of the revised manuscript)

• There is no radiologic data to show the portal vein diameter or the presence of collaterals, which is crucial to this type of study, and no fibroscan to diagnose the level of cirrhosis.

Thank you very much for your important comment. But some clinical data was missing due to the retrospective design of the study and lack of availability. What you point out was added as a limitation of this study. (at the top of the page 13 of the revised manuscript)

• QUOTE from literature (Non-cirrhotic patients more frequently present the typical endoscopic watermelon-, striped-pattern and are mainly represented by middle-aged women whereas the honeycomb-, diffuse-pattern prevails in patients with liver failure) Fuccio L, Mussetto A, Laterza L, Eusebi LH, Bazzoli F. Diagnosis and management of gastric antral vascular ectasia. World J Gastrointest Endosc. 2013 Jan 16;5(1):6-13. doi: 10.4253/wjge.v5.i1.6. PMID: 23330048; PMCID: PMC3547119.)

We missed a very important study on this topic. We cited the paper you mentioned in appropriate places. Thank you very much. (at the page 11 of the revised manuscript. REFERENCE No 23)

• Other references on the topic with similar aim: 1. Dulai GS, Jensen DM, Kovacs TO, Gralnek IM, Jutabha R. Endoscopic treatment outcomes in watermelon stomach patients with and without portal hypertension. Endoscopy. 2004 Jan;36(1):68-72. doi: 10.1055/s-2004-814112. PMID: 14722858. 2. Ito M, Uchida Y, Kamano S, Kawabata H, Nishioka M. Clinical comparisons between two subsets of gastric antral vascular ectasia. Gastrointest Endosc. 2001 Jun;53(7):764-70. doi: 10.1067/mge.2001.113922. PMID: 11375585. Discussion:

Also we missed a very important study on this topic. Thank you very much. In particular, the result of the Dulai GS, et al.'s study "Bleeding was effectively palliated by endoscopic treatment, regardless of the presence of portal hypertension." was cited in the last part of the "DISCUSSION" section. (at the bottom of the page 12 of the revised manuscript. REFERENCE No 1).

• The authors mentioned " We also found that patients with GAVE in the absence of cirrhosis more frequently had overt GI bleeding and required endoscopic treatment more frequently than those with GAVE and cirrhosis." could they discuss why and the reasons behind this?

We really respect for your very intelligent question. However, the reason for the significant difference in the incidence of GI bleeding according to the presence or absence of cirrhosis in GAVE is unclear, and other studies that reported similar results did not provide a clear explanation either. We have carefully described the possibility of their association with neurohumoral factors in the "DISCUSSION" section (at the page (bottom)11-(top)12 of the revised manuscript)

• The authors stated " The reason why we have not used the term "recurrent bleeding" is that it was unclear whether GAVE bleeding occurred at an APC treated area or an untreated remnant area or whether bleeding occurred at a new telangiectasia lesion due to GAVE extension.". You could use the term recurrent as the pathology is still present in the subsequent episodes in the bleeding and non bleeding areas (vasodilatory metabolites with telangiectasia and arteriolar dilation). This sentence is redundant please modify.

Reading your very sophisticated comments, we realized the sentences were confusing and unnecessary. We deleted the sentences.

• The authors stated "These results suggest that the vulnerability to bleeding depends on GAVE etiologies, but clinical course after overt bleeding doesn't depend on GAVE etiologies." could you elaborate and discuss more this point.

We searched for many literatures in order to explain and discuss the results. However, unfortunately, we failed to find any relevant literatures because the pathophysiologic features of GAVE are undetermined. In the "CONCLUSION" section, we described the need for additional research to find the pathophysiology mechanism of GAVE. (at the page 13 of the revised manuscript)

• Could the authors elaborate if any cirrhotic patients in their study received beta blockers as a prophylaxis?

We did not investigate beta-blockers for prevent variceal bleeding in this study because beta blocker was not investigated in the previous study. We hope your generous understanding.

Answers to Reviewer No. 05226306

(highlighted by green color in the updated version of the manuscript)

1. Would the co morbidities themselves have a significant impact on the clinical features / outcome?

The significant difference in the incidence of overt bleeding was observed in several studies including the present study according to the presence or absence of cirrhosis in GAVE. We really respect your very intellectual question. However, it is still unclear whether this different impact on the clinical features is due to co morbidities themselves or not. We have carefully described the possibility of their association with neurohumoral factors in the "DISCUSSION" section **(highlighted by yellow color)** (at the page (bottom)11-(top)12 of the revised manuscript)

2. Would the presence of CKD (5/7) be a confounding bias regarding the parameters Cr, Alb ?

Your point is very correct. Co-morbidities such as CKD and liver cirrhosis could be a confounding bias regarding several laboratory findings such as serum Cr, albumin. Comparison of laboratory findings is a univariate analysis between each group. We were unable to adjust confounding variable and to perform multivariate analysis due to the small sample size in this study.

3. How was improvement after the APC evaluated in the pts?

The endpoint of APC treatment was defined as complete or almost complete disappearance of vascular ectasia. The criteria for successful APC treatment were cessation of GI bleeding and the need for transfusion. These were described in the "*Study design and patients*" part of the "MATERIALS AND METHODS" section. (at the page 6 of the revised manuscript)

4. "it was unclear whether GAVE bleeding occurred at an APC treated area or an untreated remnant area or whether bleeding occurred at a new angioectasia lesion due to GAVE extension". How effective was APC for the GAVE lesions?

Another reviewer also mentioned that there were problems with the sentence you pointed out. We realized the sentence were confusing and deleted it.
APC was performed successfully in 10 patients with GAVE bleeding (4 patients had cirrhosis and 6 did not) and no complication was occurred. However, 8 of 10 patients required additional hospitalization due to GAVE bleeding after APC treatment and only two patients did not (one in the non-cirrhosis group and one in the cirrhosis group). These were described in "DISCUSSION" section. (at the page 12 of the revised manuscript)

5. Would a multivariate analysis help in identification of the implicating parameters?
Yes, multivariate analysis helps in identification of the implicating parameters. However, the sample size was small, especially numbers of bleedings and APC cases, and thus, it was not possible to perform further multivariate analysis. These were described as the limitation of this study in the end of "DISCUSSION" section (at the page 13 of the revised manuscript). We hope your generous understanding.

Thank you very much for your sincere reviews and comments.

Thank you again for publishing our manuscript in the *World Journal of Clinical Cases*

Sincerely yours,

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