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Title: Presence of columnar-lined esophagus is negatively associated with the presence of esophageal varices in Japanese alcoholic men

Professor Li-Juan Wei
Science Editor, World Journal of Gastroenterology

Dear Professor Wei,

We appreciate the comments by the reviewers. They have been helpful in strengthening and clarifying portions of the manuscript.

Our point by point reply is provided below:

Reviewer #1

COMMENTS TO AUTHORS

This is interesting study conducted over significant number of patients and based on the empirical observation from the authors' clinical practice that patients with CLE less frequently have EV. They tested this hypothesis among Japanese alcoholic patients by using retrospective cross-sectional design. As correctly acknowledged by the authors retrospective nature and cross-sectional design are not the best way to explore causal relationship between the two categories (i.e presence and size of EV and CLE). Nevertheless, these results are based on significant number of patients, and appropriate statistical methods have been used and therefore the results and conclusions of the study are meaningful, at least concerning the clearly established inverse correlation between the presence of CLE and EV. The observation from this study is interesting, innovative and represents the basis for the further studies which should be conducted prospectively in the longitudinal fashion to furtherly test this intriguing issue.

Reply: Thank you for your comments and your conclusion that our paper should be accepted. Based on your comments we have added the following sentences in the Discussion section:

Page 16: **In conclusion, this cross-sectional observational study revealed a negative association between the presence of CLE and the presence of EVs in Japanese alcoholic men. Further studies should be conducted prospectively in a longitudinal fashion to confirm this finding.**



Reviewer #2

COMMENTS TO AUTHORS

This manuscript from Japan is very interesting well- written but without a pathologic confirmation of the Barrett s esophagus the results are not valid.

Reply: The point made by the Reviewer is a potential limitation of the study, which was conducted based on endoscopic observations. We have added the Reviewer's point in the paragraph on limitations, as follows:

Page 16: **Pathological studies of autopsied cirrhotic subjects are warranted to clarify the pathological background underlying the negative association between the presence of CEL and the presence of EVs.**

Reviewer #3

COMMENTS TO AUTHORS

A negative observational study to describe the presence of columnar-lined esophagus is negatively associated with the presence of esophageal varices in Japanese alcoholic men and manuscript written well.

Reply: Thank you for your comments and your conclusion that our paper should be accepted.

Reviewer #4

COMMENTS TO AUTHORS

This paper explored the association columnar-lined esophagus with esophageal varices (EVs) in alcoholic men. This topic is novel. I have some comments as follows.

1. The authors concluded that "The development of CLE may impede the development of EVs, and examination for CLE may benefit alcoholics with advanced liver disease by identifying their risk for the development or progression of EVs". Although the authors provided some explanations regarding the development of CLEs and EVs in the Discussion section, the study cannot explore the orders of columnar lined esophagus and EVs. Which occurs firstly? So your conclusions should be revised.

Reply: In response to the Reviewer's comments, we have revised our conclusions as follows:

Page 16: If the observed associations between CLE and EVs and advanced EVs reflect causal relationships, the current trend toward lower *Helicobacter pylori* infection rates in Japan may



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result in lower EV rates and advanced EV rates in the future, and examination for CLE may benefit alcoholics with advanced liver disease by identifying their risk for the development or progression of EVs.

In conclusion, this cross-sectional observational study revealed a negative association between the presence of CLE and the presence of EVs in Japanese alcoholic men. Further studies should be conducted prospectively in a longitudinal fashion to confirm this finding.

2. Child-Pugh class/score is employed for the assessing the severity of liver cirrhosis. So the Child-Pugh class/score is not necessary in patients without liver cirrhosis.

Reply: The Child-Pugh classes/scores of the patients without liver cirrhosis have been deleted (Tables 1-4), and they are only used in regard to the patients with cirrhosis (Tables 5 and 6).

3. In Table 1, does the "EVs group" represent "Cirrhosis with EV" group? In other words, do all patients with EVs have liver cirrhosis? This is important because some patients had non-cirrhotic portal hypertension.

Reply: There were 6 non-cirrhotic subjects with EVs. We compared the group of subjects with EVs and the group without EVs and have added the incidence of cirrhosis in each group in Table 1. In accordance with the new Table 1, we have changed the Results section as follows: Page 11: LC without EVs was diagnosed in 152 subjects, **LC with EVs in 174 subjects, and EVs without LC in 6 subjects.** The EVs were classified as F1 in 92 subjects, F2 or F3 in 41 subjects, RC-sign-positive in 21 subjects, and post-treatment in 26 subjects, 17 of whom were reported to have been treated for variceal rupture. **All of the EVs in the subjects without LC were classified as F1.** Table 1 shows the background factors of the 1614 subjects according to whether they had EVs. There were no significant differences between **the group with EVs and the group without EVs** in age, usual alcohol consumption, smoking, hepatitis C and B infection status, or ALDH2 and ADH1B genotypes. LC, gastric varices, and higher grade PHG were more common **in the group with EVs than in the group without EVs** ($p < 0.0001$). Most of the gastric varices in the group without EVs were found in the fornix alone, and gastric varices located in the cardia or cardia plus fornix predominated in the group with EVs.

4. In Table 2, the authors combined the patients without EVs with and without cirrhosis into an individual group. The analysis might be inappropriate. The group with 1434 patients should be separated into two groups with and without liver cirrhosis.



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Reply: We have added the comparisons in the group with cirrhosis in Table 2 and have changed the Results section as follows:

Page 11: When advanced forms of EVs were defined as F2 - F3 varices, RC-sign-positive varices, and post-treatment varices, the proportion of subjects with CLE ≥ 5 mm decreased in the following order ($p < 0.0001$): 23.3% in the group without EVs, 17.4% in the group with F1 varices, and 5.7% in the group with advanced varices, and **the findings were similar in the subgroup of subjects with LC ($p = 0.0004$). The incidence of CLE ≥ 5 mm in the group of subjects with advanced EVs did not differ significantly according to whether they had or had not received endoscopic treatment (7.7% and 4.8%, respectively, $p=0.63$). The proportions with a hiatal hernia ≥ 10 mm (24.4%, 20.7%, and 13.6%, respectively) decreased in the same order as the order in which the proportions of subjects with CLE ≥ 5 mm decreased ($p = 0.017$), but the trend was not significant in the subgroup of subjects with LC.**

5. Furthermore, the comparison between patient with and without liver cirrhosis should be performed. Some new message might be provided. And then, a new comparison between cirrhotic patients with and without EVs should be performed.

Reply: In response to this important comment, we compared the background factors of the subjects according to whether they had EVs and conducted a multivariate analysis to identify the determinants of the presence of EVs in the subjects with cirrhosis. The results are shown in Table 5 and Table 6, and they were essentially the same. The very small number of subjects with EVs ($n = 6$) in the group without cirrhosis hampered the analysis in the non-cirrhosis group.

Page 12: **Table 5 shows the background factors of the 326 subjects with LC according to whether they had EVs, and there were no significant differences between the two groups in age, usual alcohol consumption, smoking, hepatitis C and B infection status, or ALDH2 and ADH1B genotypes. CLE ≥ 5 mm ($p = 0.003$), gastric varices ($p < 0.0001$), and higher grade PHG ($p < 0.0001$) were all more common in the LC group with EVs than in the LC group without EVs. Advanced Child-Pugh class ($p = 0.011$) was more common in the LC group with advanced EVs.**

A multiple logistic regression analysis showed that the ORs (95% CI) for EVs and advanced EVs **in the subgroup of subjects with LC** decreased with the presence of CLE ≥ 5 mm (0.46 [0.23-0.93] and 0.24 [0.08-0.74], respectively, vs. CLE 0-4 mm; Table 6). Child-Pugh class was not associated with EV status. The ORs for EVs and advanced EVs increased with progression of the grade of PHG, and the OR for advanced EVs increased with the presence of gastric varices.

6. In patients with post-treatment varices, some scars secondary to ligation or sclerotherapy



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might be present. If so, does it influence the development of CLE? A new analysis should be added to compare the incidence of CLE between EVs patients with and without endoscopic treatment.

Reply: In response to the Reviewer's comment, we evaluated this issue as follows:

Page 11: The incidence of CLE ≥ 5 mm in the group of subjects with advanced EVs did not differ significantly according to whether they had or had not received endoscopic treatment (7.7% and 4.8%, respectively, $p=0.63$).

Page 15: Scars secondary to endoscopic ligation or sclerotherapy were present in some of the LC subjects with post-treatment varices and their presence may have influenced the development of CLE. However, the incidence of CLE in the LC group did not differ significantly according to whether there was a history of endoscopic treatment.

7. The authors provided 2 figures. One is about the PHG, another is about CLE. However, the study focused on the EVs. So the figures regarding severity of EVs should be added. The figure legends should be a noun or phrase, but not a sentence. The present legends are not appropriate. Indeed, I do not understand the aim of the figure 2 by reading its legends. Please revise them. The endoscopists are skilled at diagnosing CLE and measuring the length of CLE. However, this paper is also learnt by the hepatologists. So the authors should add more information regarding how to diagnose with CLE and to measure the length of CLE. Similarly, the diagnosis and measurement of hiatal hernia should be also added in the figure.

Reply: We have added a figure regarding the severity of the EVs and have changed the figure legends to clarify the methods of diagnosing and measuring CLE and hiatal hernias.