March 10 , 2017

To,

The Editor,

World Journal of Gastroenterology.

Dear Editor,

Please find attached our revised manuscript entitled, "Risk of Progression of Barrett's Esophagus in patients with Cirrhosis". The manuscript ID is 32794 and is accompanied by an offer of waiving publication fee if accepted for publication.
All the authors have contributed to the conception and design, acquisition of data and drafting of manuscript. The final draft has been approved by all coauthors. The revisions are in red font. Please find the point by point responses to reviewers' comments below.

Thank you for your consideration.

Sincerely,

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1) Reviewer 01115220

The authors provide data from a case-control study examining the rate of progression in Barrett's esophagus in patients with Cirrhosis versus those without. Overall the results show a non-significant effect of cirrhosis, although this may be an underestimate of the effect as the study is seemingly underpowered to detect a significant difference. This area is certainly interesting and important and there are certainly pathophysiological links that could lead to increased rates of progression in Barrett's esophagus is cirrhotic patients. Whilst the data are overall negative, the paper is of interest, although several aspects of the design and analysis of the study do deserve further comments.

Major points: 1. The abstract is rather confusing, the aim sets this study out as a case control study examining progression in Barrett's, yet the majority of the data listed in the abstract concerns the diagnoses at the index endoscopy. This only becomes clear after reading the whole paper and this portion of the abstract should be clearer. In fact, the key data that the reader would be expected to see in the abstract - the rates of progression are not actually given at all, bit appear in the core tip instead, this should be rectified. In the abstract, 3rd line from end of results, do the authors mean statistical rather than clinical significance?

Response: The abstract has been revised as follows: There were no differences in incidence rates of HGD/EAC in nondysplastic BE between cirrhotic cases and noncirrhotic controls (1.4 vs 1.1 per 100 person- years, p=0.8) In LGD, cirrhotic patients were found to have higher rates of progression to HGD/EAC compared to control group though this did not reach statistical significance (13.7 vs 8.1 per 100 person- years, p=0.51).

2. In the Introduction, when considering the relationship between esophageal cancer and cirrhosis, are these data about all cancers or specifically about adenocarcinoma?

Response: The studies we found looked at the incidence of all documented esophageal cancers, and did not specifically report the type of cancer or the histopathology.

3. The study lacks the very important data on smoking which does increase the rate if progression and aspirin/NSAIDs and statins which seem to associated with reduced rates of progression. It may not be possible to correct for this, but these omissions need commenting on.

Response: This was included under limitations in discussion. "Also data regarding other factors such as smoking and use of medications such as aspirin, nonsteroidal anti-inflammatory drugs, proton pump inhibitors which may affect progression rates was not available."

4. Although the authors have outlined their plan for statistical analysis, they have not included a clear description of what was intended to be the primary end point for their study and have omitted to include a sample size estimate and power calculation in the methods and these data should be included.

Response: The primary end point was development of HGD/cancer in cirrhotic patients with BE and compare to controls. On retrospective review, we found 57 patients with BE and cirrhosis in our institution. Sample size calculation did not apply for this situation. We matched cases 1: 4 with controls as studies have shown that there is no further gain by adding more controls (reference: Grimes, David A et al. Compared to what? Finding controls for case-control studies. The Lancet, Volume 365, Issue 9468, 1429 – 1433)

5. There should be further discussion as to the biases which seem inherent in this study methodology. Could the authors clarify whether all the subjects were actually enrolled

in a regular Barrett's surveillance programme and what this was or were these ad hoc endoscopies? Response: Yes, they are enrolled in surveillance program

6. Could the increased pick up of progression in cirrhotics be due to more frequent endoscopy, for variceal surveillance?

Response: The follow up period appears to be same for both cases and controls; so this is not due to increased number of endoscopies. Median number of endoscopies in cirrhotic were 2 (IQR2, 4) and in controls were 3(2, 6). This information is added to Table2.

7. Do the authors have data for number of biopsies per cm of Barrett's in the two groups, it would be interesting to see if less biopsies are indeed taken in the cirrhotic group?

Response: Unfortunately, this information is not available

8. The overall rates of progression in the cohort, both cirrhosis and controls does seem high compared to the latest data (which suggests a rate of progression closer to 1:300 per year overall), the authors should comment on this. It would be very helpful if the authors reanalyzed their data and presented separately the rates of progression for cases after their first follow up endoscopy confirmed no-dysplasia. It is recognized that in many similar cohorts, early neoplastic progression actually represents lesions missed at index endoscopy and no progression. It is a very reasonable hypothesis that more cirrhotic patients would have dysplastic lesions missed at index endoscopy, perhaps because views were impaired by varices, reluctance to biopsy in portal hypertension, or arguably that a hepatologically focused endoscopist will be less effective at finding subtle dysplasia than a Barrett's expert.

Response: Thank you for pointing out this oversight. We reanalyzed the data excluding HGD and cancer within the first year as they may be prevalent cases. The revised data is incorporated in the text and in the table 3.

9. Can the authors confirm that no treatment was offered to those with LGD? Radiofrequency ablation for LGD was a viable option for the last several years of the study period, was this applied at all?

Response: No ablative treatment was offered to LGD patients in this study.

Reviewer 2: 03317317

This manuscript showed the unique aspect on development of Barrett's esophagus. To date, there have been so many reports on the same issue, but a few study have done in cirrhosis subjects. The author got a positive data on BE progression characteristic for cirrhotic subjects.

1) The presence of hiatal hernia showed a statistically significant difference in Table1, but no trend from no dysplasia to low and high grade dysplasia was seen. Only LGD group showed highest incidence of hiatal hernia compared to no and high grade dysplasia. It is difficult to think about biological and clinical significance in this data.

Response: The cases and controls were matched in terms of age, gender and body mass index; so the prevalence of hiatal hernia varied in different groups. Our study was underpowered to detect if hiatal hernia played any role in progression to dysplasia.

2) Why was the incidence of hiatal hernia lower in cirrhosis than no cirrhosis subjects in Table2?

Response: As above

Reviewer 3: 00048205

This is a well-designed retrospective study that analyzed the risk of progression of Barrett`s esophagus in patients with cirrhosis. This is an interesting topic, but there remain some questions to accept their logic. 1. Some amount of the subjects have varices, but they performed biopsy specimens based on the Seattle-protocol. However, the procedure seemed to be very dangerous, so they should demonstrate how to practically perform their procedure for the patients with varices. Is there any discrepancy in biopsy procedure between patients with varices or without varices? If so, there may be critical bias in this study. Please discuss this point.

Response: Only patients enrolled in BE surveillance program are included in the study. . Of the 16 out of 57 patients with varices, there was no complications or adverse effects such as bleeding documented during or after the procedure. Usually, the mucosa in between the variceal columns was biopsied.

2. In clinical setting, the histopathological results of some biopsy specimens should be classified as `indefinite diagnosis`. However, there is no description about this point. Is it real?

Response: BE with indefinite for dysplasia were included under LGD group as clinical management is similar. This is added to methods.

3. They demonstrated the risk of cirrhosis for the development of Barrett`s carcinogenesis, but there is no significant different in BMI, Child-Pugh score, or underlying condition. Especially, BMI seemed to be negatively associated with progression of BE to dysplasia in cirrhotic patients, instead several previous studies demonstrated positively associated with Barrett`s cancer development. Additionally,

there is a question why Child-Pugh score can be positively associated with the cancer development.

Response: On univariate analysis, hazard ratio for BMI was 0.89 with 95% CI of 0.79 and 1.02 with p-value of 0.085. This data does not support that BMI is negatively associated with progression of BE to dysplasia. The following information is presented in discussion

"Child-Pugh score may be associated with cancer development. This association is likely due to the increased levels of certain humoral factors in advanced liver disease. Studies have demonstrated that there are elevated levels of vasoactive intestinal peptide, neurotensin and nitrous oxide in cirrhotics with worsening liver function. These factors are known to lower LES pressure thereby facilitating GERD, the strongest risk factor for the development of BE".

4. Besides, smaller numbers of cirrhotic patients have hiatal hernia, but there is significant difference in the percentage of presence of hiatal hernia among patients with no dysplasia, LGD and HGD/BAC. Among them, there is highest percentage of the present of hiatal hernia in patients with LGD, compared with patients with HGD/BAC. Authors should demonstrate whether the presence of hiatal hernia may be associated with the development or not.

Response: On univariable analysis, hiatal hernia does not seem to be associated with neoplastic progression as presented in table 4 (hazard ratio1.7 (95% CI 0.28, 10.5) p-value=0.56)

5. There are numerous mistyping words in this draft. Please revise all of them.

Response: We apologize for this oversight. Typographic errors were rectified.

Reviewer 4: 02861605

1. I'm unclear about the following sentence in the core tip. "There was a high prevalence of nonalcoholic steatohepatitis or cardiac cirrhosis in cases." I think what is meant to say is that NASH and cardiac cirrhosis were the two most common causes of cirrhosis in cases as is clear in the results, but should be clarified here.

Response: It is clarified in the core tip.

2. The sentence in the abstract, "The prevalence of dysplasia in cirrhosis and controls were similar with 79% vs 68% without dysplasia; 8.8% vs 12% with low grade dysplasia (LGD) and 12.3 % vs 19.7% with HGD or EAC" is unclear. How can there be dysplasia in 68% and 79% of controls and cases, respectively? That seems high, or possibly is written in correctly and should be non-dysplastic patients, which seems to be the case as it is clearer in the results section. This sentence needs to be corrected.

Response: The sentence has been corrected as follows: The prevalence of dysplasia in cirrhosis and controls were similar with 8.8% vs 12% with low grade dysplasia (LGD) and 12.3 % vs 19.7% with HGD or EAC (p-value 0.1).

3. There is no description of pathologic assessment. Was this by one pathologist? Was this person specialized in GI pathology? Was there confirmation of dysplasia by a 2nd GI pathologist? If not this should be described in the limitations.

Response: All cases of suspected dysplasia were evaluated by a gastrointestinal pathologist and confirmed by a second gastrointestinal pathologist or at pathology consensus conference

4. In the results, it says, "The mean CP score was 1.3 ±0.56 and …" It's unclear how the mean CP score can be ~1 as described in the results as the minimum score is 5.

Response: We apologize for this error. It is CP class rather than score. This was changed throughout the manuscript

5. How do you explain the findings in the univariate analysis of a trend toward neoplastic progression with lower BMI and no association seen with age, length, etc.? Other studies have shown progression of dysplasia in non-dysplastic BE with BMI (Scand J Gastroenterol. 2016 Nov; 51(11):1288-93) and BE segment length (Clin Gastroenterol Hepatol. 2013 Nov; 11(11):1430-6.). The current study findings should be reconciled with prior literature in the discussion.

Response: Even though this study includes a large group of patients with BE and cirrhosis, we did not notice any effect of BMI, age, BE length on progression. This could be due to type II error.

6. A comment in the discussion in regards to the clinical dilemma of diagnosing and treating dysplastic BE in higher CP cirrhotic patients would be helpful and interesting.

Response: The following is added:

In addition, bleeding diathesis and portal hypertension in cirrhotic patients may increase the risk of bleeding complications during endoscopic eradication therapies for BE associated dysplasia. Correction of these factors is essential before any therapeutic interventions are contemplated.

Reviewer 5: 03262700

Dear Authors, Thank you for conducting this valuable project. I read your article with great interest. It is studying the characteristics of BE in cirrhotic patients and a possible link between cirrhosis and Barrett's esophagus' malignant progression. The article is well written and its structure is good. However, I need the following minor corrections to be made:

1) Comment: please replace "logistic analysis" with "logistic regression"; please expand "IQR"

Response: These changes have been made.

2) Comment: Manuscript's body: please make sure the words "MELD-Na" & "Child-Pugh" are correctly written (Hyphen, Capitalization,) throughout the text.

Response: These changes have been made.

3) Comment: In the introduction section paragraph 2, please correct the word order of "(incidence ratio: 5.6-9.8; CI: 95%)"

Response: This was corrected.

4) Comment: In the discussion section paragraph 7, please complete "As this a retrospective study…." with a suitable verb.

Response: The verb "is" is added.

5) Comment: Table 1: please remove the statistical tests' names and mention them in the manuscript's body (where the study's statistical method is explained)

Response: This has been removed from under the table.

6) Comment :Please expand MELD-Na under the table; please correct capitalization of SteatoHepatitis; please add a measurement unit for hiatal hernia length; please replace [P25,P75] with (25th, 75th percentile).; Table 2: please insert a measurement unit for BMI and BE length; please change the percentages of ethnicity subgroups as percentages are not "(column %)" probably due to missing values; please replace [P25,P75] with (25th, 75th percentile).Table 3: please explain at the bottom of the table how data are shown. Table 4: please expand BE, MELD-Na and HR at the bottom of the table. In all tables please label statistically significant p values with an asterisk and place "* statistically significant" at the bottom of the table.

Response: All the above changes have been made.

Reviewer 6: 03219312

This is an interesting study on BE and Cirrhosis. I do have a few minor comments on the presentation of the results that can be addressed.

1) I would adjust the y-axis scale in Figure 1 (do not go all the way to 100%) to make the two lines more legible.

Response: Figure 1 revised.

2) Table 1--I would present the Age results as medians and interquartile ranges. Derive p-values with the Kruskal Wallis test.

Response: These changes are made in Table1.

3) There are no power calculations (it is optional in my opinion to provide them) and one limitation you do not stress is the sample size. You should emphasize that a larger study on a more diverse population of BE patients would yield more definitive results.

Response: This is included under limitations

4) I would do a more thorough literature review for the Discussion section on alcohol and BE. One paper that found no relationship between BE length and alcoholism is: Navab F, Nathanson BH, Desilets DJ. The impact of lifestyle on Barrett's Esophagus: A precursor to esophageal adenocarcinoma. Cancer epidemiology. 2015 Dec 31; 39(6):885-91. Another paper that somewhat contradicts your findings is: Anderson LA, Cantwell MM, Watson RP, Johnston BT, Murphy SJ, Ferguson HR, McGuigan J, Comber H, Reynolds JV, Murray LJ. The association between alcohol and reflux esophagitis, Barrett's esophagus, and esophageal adenocarcinoma. Gastroenterology. 2009 Mar 31; 136(3):799-805. I would consider (this is optional) adding them to your Discussion or references. I

am sure there are others out there. Again, a more thorough literature review will be helpful here.

Response: The following is added to discussion:

Although alcohol accounts for over 60% cases of cirrhosis in US population, it was the main etiological factor in only 14.3% of cases of BE with cirrhosis in our study. Whether this is due to the protective effects of alcohol on BE is uncertain as some studies show lack of effect and others show a slight protective effect. (Reference: 1:Navab F, Nathanson BH, Desilets DJ. The impact of lifestyle on Barrett's Esophagus: A precursor to esophageal adenocarcinoma. Cancer epidemiology. 2015 Dec 31;39(6):885-91. 2) Anderson LA, Cantwell MM, Watson RP, Johnston BT, Murphy SJ, Ferguson HR, McGuigan J, Comber H, Reynolds JV, Murray LJ. The association between alcohol and reflux esophagitis, Barrett's esophagus, and esophageal adenocarcinoma. Gastroenterology. 2009 Mar 31; 136(3):799-805. 3)Xu Q, Guo W, Shi X, Zhang W, Zhang T, Wu C, Lu J, Wang R, Zhao Y, Ma X, He J. Association Between Alcohol Consumption and the Risk of Barrett's Esophagus: A Meta-Analysis of Observational Studies. Medicine (Baltimore). 2015 Aug; 94(32):e1244. doi: 10.1097/MD.0000000000001244. PMID: 26266354).