

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 32794

Title: Risk of Progression of Barrett's Esophagus in Patients with Cirrhosis

Reviewer's code: 03219312

Reviewer's country: United States

Science editor: Yuan Qi

Date sent for review: 2017-01-27 20:49

Date reviewed: 2017-01-28 07:03

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

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



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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.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 32794

Title: Risk of Progression of Barrett's Esophagus in Patients with Cirrhosis

Reviewer's code: 03262700

Reviewer's country: Iran

Science editor: Yuan Qi

Date sent for review: 2017-01-27 20:49

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input checked="" type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

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- Abstract: please replace "logistic analysis" with "logistic regression"; please expand "IQR". 2- Manuscript's body: please make sure the words "MELD-Na" & "Child-Pugh" are correctly written (Hyphen, Capitalization, ...) throughout the text; in the introduction section paragraph 2, please correct the word order of "(incidence ratio: 5.6-9.8; CI: 95%)"; in the discussion section paragraph 7, please complete "As this a retrospective study...." with a suitable verb. 3- Tables: Table 1: please remove the statistical tests' names and mention them in the manuscript's body (where the study's statistical method is explained); 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



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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. No other major criticism. Thank you

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 32794

Title: Risk of Progression of Barrett's Esophagus in Patients with Cirrhosis

Reviewer's code: 02861605

Reviewer's country: United States

Science editor: Yuan Qi

Date sent for review: 2017-01-27 20:49

Date reviewed: 2017-02-02 03:29

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

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. 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. 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. 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. 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?



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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. 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.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 32794

Title: Risk of Progression of Barrett's Esophagus in Patients with Cirrhosis

Reviewer's code: 00048205

Reviewer's country: Japan

Science editor: Yuan Qi

Date sent for review: 2017-01-27 20:49

Date reviewed: 2017-02-07 22:17

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input checked="" type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

Comments to the Author 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. 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? 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. 4.



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

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 32794

Title: Risk of Progression of Barrett's Esophagus in Patients with Cirrhosis

Reviewer's code: 03317317

Reviewer's country: Japan

Science editor: Yuan Qi

Date sent for review: 2017-01-27 20:49

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
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<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Plagiarism	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

Risk of Progression of Barrett's Esophagus in patients with Cirrhosis Tehilla Apfel et al 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. #2 Why was the incidence of hiatal hernia lower in cirrhosis than no cirrhosis subjects in Table2?

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 32794

Title: Risk of Progression of Barrett's Esophagus in Patients with Cirrhosis

Reviewer's code: 01115220

Reviewer's country: United Kingdom

Science editor: Yuan Qi

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

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 in 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, but 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? 2. In the Introduction, when considering the relationship

between esophageal cancer and cirrhosis, are these data about all cancers or specifically about adenocarcinoma? 3. The study lacks the very important data on smoking which does increase the rate of progression and aspirin/NSAIDs and statins which seem to be associated with reduced rates of progression. It may not be possible to correct for this, but these omissions need commenting on. 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. 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? Could the increased pick up of progression in cirrhotics be due to more frequent endoscopy, for variceal surveillance? 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? 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 reanalysed their data and presented separately the rates of progression for cases after their first follow up endoscopy confirmed no-dysplasia. It is recognised 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. 6. 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?