

May 7, 2019

Dr. Jia-Ping Yan
Science Editor, World Journal of Gastroenterology

Dear Dr. Yan and members of the Editorial Board,

Thank you for giving us the opportunity to resubmit our manuscript entitled “**Ongoing GERD symptoms and obesity are more common among patients with early Barrett’s neoplasia under 50 years of age.**” (47913) to World Journal of Gastroenterology.

I would like to thank the editors and reviewers for the valuable input. Your comments and those of the reviewers have all been helpful in allowing us to revise our paper. All changes have been highlighted in red text in the resubmitted manuscript. We have attempted to address the questions raised by the reviewers in another file.

Yours sincerely

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Point by point responses to reviewers' can be found below.

Science Editor, Jia-Ping Yan

Please don't include the abbreviations in the title.

The title should be no more than 12 words.

→ **Thank you for your valuable comment. We changed the title as below,
"Clinical characteristics of young patients with early Barrett's neoplasia."**

Reviewer #1 (00036194)

I realise that your study was retrospective but, in future, a validated reflux questionnaire would be appropriate to determine frequency and severity of reflux symptoms.

→ **Thank you for your valuable comment. We totally agree with your suggestion. Unfortunately we could not include the results of such questionnaire in this study. Further studies are needed to evaluate it.**

Reviewer #2 (03259368)

The authors present an interesting study and should be commended for their work. Iwaya Y et al. aim to assess Early Barrett's neoplasia in young patients. This study adds to the literature. The topic is very interesting and important. I do agree with the conclusion of the paper based on their results. The paper is well structured and well written. I have minor comments: The paper has no comparison group and is purely descriptive. This has been clearly addressed in the discussion. Smoking is protective in the multivariate analysis. Please comment. I suggest acceptance after addressing these minor comments. Congratulations to this paper.

→ **Thank you for your useful comments and suggestions. As you mentioned, we did not have comparison group and our paper is descriptive, which is our study's limitation. According to your comment, we have emphasized that point in DISCUSSION part (Page 15. Line 9). In terms of smoking, firstly we have to apologize to you for this misleading part. We did not mean smoking has protective role for EAC among young patients but smoking should have more important role for Barrett's carcinogenesis among older group. We think that this result is caused by the accumulation effect of toxicity for a longer time span of smoking. We added a sentence mentioning it in the DISCUSSION part (Page 14. Line 7).**

Reviewer #3 (02535775)

To Authors, The article titled “Ongoing GERD symptoms and obesity are more common among patients with early Barrett’s neoplasia under 50 years of age” was reviewed. This study has been giving us clear results about the importance of early diagnosis of Barrett’s esophagus and Esophageal Adenocarcinoma in people who are younger than 50 years of age. On the other hand, it creates a new perspective for guidelines. This study deserves to publishing in priority.

→**Thank you for your kind comment. We really appreciate it.**

Reviewer #4 (02908500)

The paper entitled: “Ongoing GERD symptoms and obesity are more common among patients with early Barrett’s neoplasia under 50 years of age” is a very nice paper. It has a good number of patients but it is retrospective and the follow-up period is not so long. Why it was the follow-up only one year? However, the results are interesting. I have some specific comments. In the group of patients >50 years there a lot of those with diabetes and hypertension, two conditions which associate dyslipidemia. How do you interpret in table 1 the result for treatment with statins? Are there a relationship between GERD, Barrett’s neoplasia and the treatment with statins?

→**Thank you for your valuable comments. First, the follow-up period was not only one year. We meant that we included only the patients followed up for more than 12 months. According to your comment, we rewrite this part (Page 9. Line 24). And in terms of statins, statins have shown a protective effect against cancer in many studies. But in this study, we think why older patients had higher prevalence of taking statin was just due to aging. Older patients should have higher prevalence accompanying metabolic syndromes rather than young counterpart and there is no doubt that such older patients are more likely to have hyperlipidemia. We cannot conclude that there is any relationship between GERD, Barrett’s neoplasia and the treatment with statins from our study. We added a sentence mentioning it in the DISCUSSION part (Page 14. Line 21).**

Reviewer #5 (02908500)

This is a well written manuscript summarizing the findings of a retrospective analysis of a prospectively maintained database comprised of consecutive patients with early-stage esophageal and high grade dysplasia at a tertiary-referral center between 2001 and 2017. The conclusion of the paper is to recommend BE screening in patients <50 years of age, if they suffer from obesity and GERD symptoms. The findings that obesity is linked to Barrett's or neoplasia is younger patients has been reported previously (Assessment of familiarity, obesity, and other risk factors for early age of cancer diagnosis in adenocarcinomas of the esophagus and gastroesophageal junction. Chak A1, Falk G, Grady WM, Kinnard M, Elston R, Mittal S, King JF, Willis JE, Kondru A, Brock W, Barnholtz-Sloan J-AJ Gastroenterology 2009). The additional observation is that younger patients

tend to suffer from GERD more frequently than older patients. One of the possibilities mentioned in the paper to explain the observed increases in BE and esophageal neoplasia is the eradication of *H pylori*. Did the patients in the study undergo *H pylori* testing or treatment? It would have been informative to know.

→**Thank you for your valuable comment. Unfortunately, we don't have the data of *H.pylori* testing or treatment. But your comment is very suggestive. We will include these data in next study as possible as we could.**

The long term follow up of patients is also lacking and the final outcome of the differences between old and young patients is unknown. There is no mention about morbidity and mortality (may be because the follow up was only for 1 year although the population was followed over 16 years)

→**We have to apologize to you for this misleading part. The follow-up period was not only one year. We meant that we included only the patients followed up for more than 12 months. According to your comment, we rewrite this part (Page 9. Line 24). In terms of morbidity and mortality, as we mentioned in limitation section, we had some patients lost to follow-up due to the retrospective nature, therefore we don't have such data. We added a comment mentioning the lack of morbidity and mortality data (Page 15. Line 15).**

Minor comments: Page 11 "Indeed, our data revealed that the percentage of young early-stage EAC/HGD patients was significant (10%). Please specify that the percentage is in your patient population. Page 10: "Figure 1" should be Table 1 Page 6 : "Early-stage stage". Delete stage

→**Thank you for your valuable comments. We changed these parts that you pointed out.**