RESPONSE TO REVIEWERS

Thank you for taking time to review our paper. We indeed appreciate the reviewer's constructive comments and suggestions. Without your comments, this manuscript would not be improved further. We have revised the manuscript accordingly and our responses to the reviewer's comments are as follows.

Reviewer 1 (code: 03475239):

interesting study which is well-written

Reply: Thanks for your appreciation.

Reviewer 2 (code: 00058381):

Major Comment: The clinical conclusion ("Our findings remind us to pay more attention to those high-risk patients when they undergo an UGI panendoscopy") is vague and should be more concrete. What is exactly meant by "paying more attention"?

Minor Comment: In spite of editing, there are some linguistic/stylistic problems in the text (e.g., section "Criteria and Definitions": "There was also a possibility that patient who received endoscopic procedures but was not included in the NHI database."; "Discussion" section: "Another possibility may be that some patients receiving invasive procedures were prescribed prophylactic antibiotics or had concurrent used antibiotics, thus preventing PLA development since their use has been recommended for invasive procedures with a high risk of bacteremia."; Table 1: "Demographic and Comorbidities of Pyogenic Liver Abscess Cases and Controls").

Reply: Thanks for your suggestion. We have revised the text as follow:

For major comment:

Page 14.

In conclusion, a higher risk of PLA was found in patients who had recently undergone an UGI panendoscopy, especially within the first 10 d after

panendoscopy. Clinical physician should not ignore the risk of development of PLA after patients receiving an UGI panendoscopy, especially in those with diabetes mellitus, ESRD, liver cirrhosis, BTI, and GI malignancies.

For minor comment:

Section "Criteria and Definitions", Page 8

There was also a possibility that the patients who received endoscopic procedures were not recorded in the NHI database.

Section "Discussion", Page 12

Another possibility may be that some patients receiving invasive procedures were prescribed with prophylactic antibiotics or had concurrent antibiotics usage. Thus it prevented the development of PLA, since the use of antibiotics has been recommended for invasive procedures with a high risk of bacteremia[20, 21, 37].

Table 1 title

Table 1. Demographic Features and Comorbidities of Pyogenic Liver Abscess Cases and Controls.

Reviewer 3 (code: 03537908):

The manuscript entitled "A Recent Upper Gastrointestinal Panendoscopy Increases the Risk of Pyogenic Liver Abscess". The study aims to determine the relationship between recent gastrointestinal endoscopies and developing of pyogenic liver abscess by diagnostic coding by using Taiwan National Health Insurance Research Database. Authors analyzed big secondary data on pyogenic liver abscess and determined the risk factors. The major strength of the study is the large number of cases and coverage of all over the country. However, there are some limitations of the study according to the nature of secondary database such as lack of clinical details and limited the analysis of the association among causative pathogens. However, the study point out the potential association between upper gastrointestinal endoscopies and pyogenic liver abscess.

Comments #1. Discussion (Page 17): "UGI panendoscopy was significantly

associated with a subsequent risk of PLA" Authors should discuss about the possibility of early presentation of PLA in some cases might present with UGI symptoms and those patients then get UGI panendoscopy.

Reply: Thanks for your constructive suggestion. As Reviewer's comment, there is really a possibility that a PLA coincidentally exists when receiving panendoscopy. I have added this point into the discussion.

Discussion-Page 11

Previous studies have shown that bacteremia occurred mostly within 30 min after GI endoscopy[21]. In the present study, we found that 33.1% of PLA occurred within 10 d after an UGI panendoscopy. In addition, UGI panendoscopy in the previous 90 d had higher OR for PLA than the previous 180 d and 1 y panendoscopy. As the PLA occurred after UGI panendoscopy and the OR subsided with time, a causal relationship between them is very likely. Though the mean duration that PLA occurred after an UGI panendoscopy was 32 d (median 25.5 d), the shortest duration of finding the PLA after panendoscopy was only 1 d. Therefore, the possibility of a PLA coincidentally exists when receiving panendoscopy could not be ignored, because some patients with early PLA may also present upper GI symptoms which lead them to receive an UGI panendoscopy. The reasonable incubation time of developing PLA after panendoscopy is an interesting and important issue and deserves further study.

Reviewer 4 (code: 03494395):

This manuscript provides the updated evidence to the readers. The topic is an important one and deserves a practical value. Other risk factors for pyogenic Liver Abscess can be included, such as splenectomy, appendectomy, zolpidem Use, and herpes zoster. Four papers can be cited.

1. **Lai SW, Lai HC, Lin CL, Liao KF. Splenectomy Correlates With Increased Risk of Pyogenic Liver Abscess: A Nationwide Cohort Study in Taiwan. J Epidemiol. 2015;25:561-6.**

2. **Liao KF, Lin CL, Lai SW, Chen WC. Zolpidem Use Associated With Increased Risk of Pyogenic Liver Abscess: A Case-Control Study in Taiwan. Medicine. 2015;94:0000000000001302.**
3. **Liao KF, Lai SW, Lin CL, Chien SH. Appendectomy correlates with increased risk of pyogenic liver abscess: A population-based cohort study in Taiwan. Medicine. 2016;95:e4015.**
4. **Shen ML, Liao KF, Tsai SM, Lin CL, Lai SW. Herpes zoster correlates with pyogenic liver abscesses in Taiwan. Biomedicine. 2016;6:22.**

Reply: Thanks for your appreciation.
We have included and cited the above associated paper into our discussion and references.

Discussion – Page: 12

PLA secondary to inflammatory diseases of the GI tract, like acute appendicitis or diverticulitis, have been described in serial case reports through the mechanism of portal bacteremia[25-29], but scarcely studies have verified their association. Recently, one study demonstrated appendectomy correlates with increased risk of PLA[38]. In our study, we identified patients with a diagnosis of acute appendicitis or diverticulitis during the 15 months before having PLA.