Responses to the peer reviewers' comments

RE: Submission ID: 52932; Title: **Results of Meta-analysis should be treated critically**

Dear Editor

Thank you very much for your letter of inviting us to submit a revised version of the above-mentioned manuscript. We have revised the paper according to reviewer's suggestions. Below are our specific responses to the reviewers'comments.

Reviewer #1:

I have the following comment. 1. Please mark the abbreviation of the words at the beginning of the text, e.g., proton pump inhibitors (PPI), hepatic encephalopathy (HE).

Response：Thank you for your professional suggestion. We have made the appropriate changes in the text, such as proton pump inhibitors (PPI), hepatic encephalopathy (HE).

Reviewer #2:

I do not understand the relevance of this Letter. The bigger question is, "In whom does the risk of Hepatic Encephalopathy increase with the use of PPIs?" Millions of patients are prescribed and are on PPIs everyday. However, in my 16 years as a Hepato-pancreato-biliary and liver transplant surgeon, I have never encountered a case of Hepatic encephalopathy due to a PPI! Thus, while it is fair to point out the errors of the study by Ma et al., the clinical relevance of that meta-analysis and this letter need to be questioned.

Response： Thank you for your professional suggestion. In fact, accumulating epidemiological studies have investigated the association of proton pump inhibitors (PPIs) use with the risk of Hepatic encephalopathy (HE). Some studies have found that PPI use increases HE risk in patients with liver disease. However, other studies have suggested that PPI use has no clear relationship with HE. So far, three meta - analyses have confirmed that PPI use increases HE risk in patients with liver disease, which is consistent with the results of our letter. Of course, High-quality prospective studies are warranted to confirm these finding and further investigate the association between PPI and HE.

Reviewer #3:

Thank you for identifying critical issues of meta-analysis. This issue of interpreting heterogeneity analysis results is crucial. Neither Q nor I^2 tests are explanatory. For example, we cannot estimate how much difference is between I^2=14% and I^2=57% or 61%. Automate calculation of I^2 95%CIs is not available and the calculation is cumbersome. For conservative

estimations, a priori use of random effects model analysis can be recommended. Please clarify what is the difference between the 2 analysis presented in the letter.

Response：We are very grateful for your professional evaluation. The fixed effect model assumes that all the included studies have the same true effect size, while the true effect size in the random effect model varies with different studies. When the observed effect size of each study approaches or equals its true effect size, the heterogeneity is not obvious and the fixed effect model should be used; otherwise, the random effects model was used. The Cochrane Handbook has stated that when I^2 is less than 40%, a fixed effects model should be used for meta-analysis; Otherwise, a random effect model should be used. In general, the conclusions obtained by random effects models tend to be conservative. Therefore, a random effects model can be used in any case. However, when the heterogeneity is significant, only the random effect model can be used and further analysis is needed to find the sources of heterogeneity.