

Dear editor:

Our revised manuscript (NO:78027, Meta-Analysis) entitled "Combining Chemotherapy with Targeted Therapy for Advanced Biliary Tract Cancer: A systematic review and meta-analysis" is re-submitted for publication in *World Journal of Gastrointestinal Oncology*.

I really apologize for the delay in revising the manuscript and the weaknesses in the manuscript. I greatly appreciate both your help and that of the reviewers concerning improvement to this paper. We have studied these comments carefully and have made correction which we hope meet with both you and the reviewers' approval.

We would like to express our great appreciation to you and reviewers for comments on our paper. Looking forward to hearing from you.

Sincerely,

Xiao-Dong He

Peking Union Medical College Hospital, China Academy of Medical Science & Peking Union Medical College

## **Reviewers' Comments**

**Reviewer #1:**

**Scientific Quality: Grade B (Very good)**

**Language Quality: Grade A (Priority publishing)**

**Conclusion: Accept (General priority)**

**Specific Comments to Authors:** It is a well structured manuscript and an interesting topic.

**Response:**

Thank you for your review of our paper. We really appreciate to receive the favorable comment.

**Reviewer #2:**

**Scientific Quality: Grade C (Good)**

**Language Quality: Grade B (Minor language polishing)**

**Conclusion: Minor revision**

**Specific Comments to Authors:** This is an interesting RCT meta-analysis. Please analyze whether these results are affected by biliary drainage.

**Response:**

Thank you for your positive comments and constructive suggestion. As you considered, liver dysfunction and elevated bilirubin are common problems in patients with biliary malignancies. According to NCCN guidelines ([www.nccn.org](http://www.nccn.org)), improvement of biliary drainage and liver function is pivotal for this part of patients. Previous studies have demonstrated that elevated bilirubin level was associated with increased toxicity of chemotherapy for biliary tract cancer. (DOI:10.1200/JCO.2000.18.14.2780) Thereinto, the patients with high level of bilirubin or biliary obstruction are always excluded from the clinical trials due to its

potential hepatotoxicity (DOI: 10.1016/j.ejca.2015.05.018).

On the one hand, adequate biliary drainage and organ function were required for inclusion in all the studies included in our meta-analysis. The criteria of inclusion and exclusion were consistent across studies. On the other hand, only 12 patients in the study of Juan W Valle, 2015 (7 in the Cediranib plus CisGem group and 5 in the CisGem group) and 32 patients in the study of David Malka, 2014 (15 in the cetuximab plus GemOx group and 17 patients in the GemOx group) were reported to have received treatment of biliary stents. The proportion was very low and balanced between groups. For the above reasons, we believe these results are reliable and credible, which are not affected by the condition of biliary drainage.

Unfortunately, no available data and corresponding clinical information for patients underwent biliary drainage were provided in these studies, which make it difficult to perform subgroup analyses of biliary drainage. In the future, we will pay attention to relevant clinical research and further explore its impact on patients with advanced biliary tract cancers.

Once again, thank you very much for your warm work earnestly.

**Reviewer #3:**

**Scientific Quality: Grade B (Very good)**

**Language Quality: Grade B (Minor language polishing)**

**Conclusion: Minor revision**

**Specific Comments to Authors: Minor comment The authors should modify title carried out term of "systematic review and meta-analysis". Congratulations on your excellent work.**

**Response:**

Thank you very much for your approval. We modified the title of our manuscript as suggested by you.

## **EDITORIAL OFFICE'S COMMENTS**

**(1) Science editor:**

The manuscript has been peer-reviewed, and it's ready for the first decision.

**Language Quality: Grade B (Minor language polishing)**

**Scientific Quality: Grade B (Very good)**

**(2) Company editor-in-chief:**

I recommend the manuscript to be published in the World Journal of Gastrointestinal Oncology. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it,

upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.

**Response:**

Thank you for your careful review and kind suggestions. We performed a systematic search literature again, and another researcher (Jie-Min Chen) conducted the assessment for the searched studies based on our previously stated screening criteria. Although no more recent studies could be included in this meta-analysis, the recent cutting-edge progress in the field of first-line treatment for biliary tract cancer was retrieved by the tool "the Reference Citation Analysis (RCA)", and we supplemented the relevant content in the manuscript. Extensive editing was conducted by a native speaker from the recommend professional English language editing company and the revised manuscript was submitted.

In addition, we invited another statistical expert Haiyu Pang (panghaiyu01@126.com), from the Department of Bioinformation and Epidemiological Statistics, Peking Union Medical College Hospital, to help review the statistical methods and results of the article.

Thanks again to the reviewers and editors on suggesting to further improve this manuscript, we have studied comments carefully and have made corresponding corrections which we hope meet with approval.