

Response to reviewers

Dear Editor and Reviewers,

Thank you for offering us an opportunity to improve the quality of our submitted manuscript "**Prognostic Role of Serum Carcinoembryonic Antigen in Patients Receiving Liver Resection for Colorectal Cancer Liver Metastasis: A Meta-analysis**"

(87284). We appreciated very much the reviewers' constructive and insightful comments.

In this revision, we have addressed all of these suggestions. We hope the revised manuscript has now met the publication standard of your journal.

We highlighted all the revisions in yellow colour.

On the next pages, our point-to-point responses to the queries raised by the reviewers are listed.

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This meta-analysis is significant in that it embodies what many surgeons feel is vague. While reading this manuscript, I would like to know the reason why elevated pre- and post-LR CEA levels were correlated with poor OS, DFS and RFS. It would be great if we could know the organ, timing, and form of recurrence in cases with high CEA compared to others. As for pre- and postoperative CEA, there might be some effects of neoadjuvant or adjuvant chemotherapy. In this meta-analysis, it would be difficult to make it clear, but if there are some papers, please show it in discussion.

Response: We really appreciate your suggestions. We have revised the article based on the issues you have pointed out. In the revised draft, we highlighted all the revisions in yellow color. We hope that the corrections we made will be recognized.

1. Comment. This meta-analysis is significant in that it embodies what many surgeons feel is vague.

Response: Many thanks for your suggestions. As you said, the significance of this meta-analysis is to provide a scientific basis for further improving the prognosis of patients with CRCLM in the future, to better assist surgeons in developing highly effective treatment regimens that will reduce the burden on patients and improve their survival rates.

2. Comment. While reading this manuscript, I would like to know the reason why elevated pre- and post-LR CEA levels were correlated with poor OS, DFS and RFS.

Response: We are much obliged to you for your suggestions. As described in lines 288-294 of paragraph 1 of our Discussion section, this section analyzed the relationship between the CEA and the poor OS, DFS and RFS. The main reasons for this was summarized in 3 areas, firstly: CEA protects circulating colon cancer cells from death in the blood or prevents circulating cell death as a general inhibitor of anoikis; second, it binds to the heterogeneous nuclear RNA binding protein M4 (hnRNP M4), a receptor protein in macrophages (Kupffer cells) that protect the liver, and activates Kupffer cells to secrete various cytokines that alter the liver microenvironment to facilitate cancer cell survival; third, CEA upregulates cell adhesion molecules for metastasis, such as promoting migration of colorectal cancer cells, especially to the liver, which can be measured in the serum of cancer patients. Therefore, measurement of serum CEA levels can predict the occurrence, progression, and prognosis of cancer before and after LR by indicators such as OS, DFS, and RFS.

3. Comment. It would be great if we could know the organ, timing, and form of recurrence in cases with high CEA compared to others.

Response: We are very grateful for your suggestions. In line 316 of paragraph 3 of the Discussion section, we described that high CEA levels can also be used as specific markers for lung, breast, thyroid, and other cancers. In line 322 of paragraph 3 of the Discussion section, we added a comparison of CEA levels in patients with different cancers in terms of prediction time. In line 319 of paragraph 3 of the Discussion section, we described that CEA levels can be a predictor of early recurrence in patients with CRCLM, but this study has not analyzed recurrence-related

outcome indicators. We will include more high-quality literature on this topic in the future. We add this to the discussion of limitations.

4. Comment. As for pre- and postoperative CEA, there might be some effects of neoadjuvant or adjuvant chemotherapy. In this meta-analysis, it would be difficult to make it clear, but if there are some papers, please show it in discussion.

Response: Many thanks for your suggestions. We have added references about the impact of CEA levels due to neoadjuvant chemotherapy or adjuvant chemotherapy and discussed them in the Discussion section, line 311.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: Comments/Suggestions: (1) This manuscript deals with the prognostic role of serum Carcinoembryonic Antigen in patients receiving liver resection for colorectal cancer liver metastasis. It does not break new ground, but provides a meta-analysis of previous publications. (2) The evaluation is limited by the data available in the literature. (3) Further research on the cut-off value is needed. (4) Introduction, first paragraph, last sentence: "The incidence and mortality at 30 days after LR were reported to be 14-55% and 0-11.9%, respectively, with a 5-year survival rate of only about 30-50% and a recurrence rate of up to 60% [10-12], so it will be valuable to find appropriate prognostic markers to predict the outcome in CRCLM patients after LR." – The incidence of what? (5) Discussion, first paragraph, fifth sentence: "OS-and..." -> OS and... (6) Discussion, fourth sentence from the end of the first paragraph: "...it protects circulating colon cancer cells from death in the blood or prevents circulating cell death by inhibiting the anus..." – please clarify this statement. (7) Conclusion: "There correlation between CEA levels and survival." – This sentence is incomplete, please correct it. (8) Last sentence of the text: "Therefore, based on the results of this study, high preoperative or postoperative serum CEA levels were correlated with poor prognosis, especially poor OS, in CRCLM patients who have received LR." – "Therefore" should be omitted here. (9) Reference list: Capital letters should be used in journal names (and they should be abbreviated); e.g., "World journal of gastroenterology" -> World J Gastroenterol. (10) In parts, the format of the references is not consistent with the guidelines of the journal. (11) Figures and Tables: For the publications, the citation numbers corresponding to the reference list should be added. (12) Figure 1: There should be a colon (:) after "Duplicate records removed (n=2424)". (13) Figure 2: For the readers, it should be stated why "Arru" is contained twice. (14) Figure 2 and Table 1: There are publications by Reddy from 2008 and 2009 in Figure 2 and Table 1, but two by Reddy from 2009 in the reference list. (15) Figure 4: For the readers, it should be stated why "Kawahara" is contained twice.

Response: Thank you for your valuable comments and suggestions. We used this feedback to improve the quality of our manuscripts, which provides a deeper understanding of our research. In the revised draft, we highlighted all the revisions in yellow color.

(1) Comment. This manuscript deals with the prognostic role of serum Carcinoembryonic Antigen in patients receiving liver resection for colorectal cancer liver metastasis. It does not break new ground, but provides a meta-analysis of previous publications.

Response: We are very grateful for your professional comments on this study, which helped to improve our article. We consider this study to be innovative and research-intensive. Currently there is still no meta-analysis of the correlation between serum CEA and prognosis of CRCLM. Therefore, this was the first meta-analysis to investigate the effect of pre- and post-LR serum CEA levels on prognosis in CRCLM patients.

(2) Comment. The evaluation is limited by the data available in the literature.

Response: We sincerely appreciate your suggestions. As you suggested, in line 333 of the article, we described the limitations of the available data. Up to the search date, there were fewer original published studies on the role of postoperative serum CEA in predicting patient prognosis.

(3) Comment. Further research on the cut-off value is needed.

Response: Thank you very much for your suggestions. We classified the threshold (cut-off) of serum CEA levels. Before LR, serum CEA level was divided into 4 sections in the OS group, which were ≤ 5 ng/ml, 5-50 ng/ml, 100 ng/ml, and 200 ng/ml. The results showed that increased serum CEA level was significantly associated with poor OS ($P < 0.05$). In the outcome index RFS group, serum CEA level was divided into 3 sections, ≤ 5 ng/ml, 5-50 ng/ml, and 200 ng/ml. The results showed that increased serum CEA level was significantly associated with poor RFS ($P < 0.05$); after LR, serum CEA level in the outcome index OS group was divided into 3 sections, which were ≤ 5 ng/ml, 5-50 ng/ml, and 200 ng/ml. The results showed that increased serum CEA levels were significantly associated with poor OS ($p < 0.05$). This grouping did not divide the pre-LR serum CEA level in the DFS group because it did not differ from the previous group.

(4) Comment. Introduction, first paragraph, last sentence: "The incidence and mortality at 30 days after LR were reported to be 14-55% and 0-11.9%, respectively, with a 5-year survival rate of only about 30-50% and a recurrence rate of up to 60% [10-12], so it will be valuable to find appropriate prognostic markers to predict the outcome in CRCLM patients after LR." – The incidence of what?

Response: We apologized for our careless error and thank you for your kind reminder. Morbidity here is the incidence of postoperative complications after LR, as quoted in reference 10, the first sentence in the fourth paragraph of the Discussion section.

(5) Comment. Discussion, first paragraph, fifth sentence: "OS-and..." -> OS and...

Response: We sincerely thank you for your careful reading. In accordance with your suggestion, we have corrected "OS-and..." to "OS and..."

(6) Comment. Discussion, fourth sentence from the end of the first paragraph: "...it protects circulating colon cancer cells from death in the blood or prevents circulating cell death by inhibiting the anus..." – please clarify this statement.

Response: Thank you for the correction. After careful review of the reference, we have corrected it to "...it protects circulating colon cancer cells from death in the blood or prevents circulating cell death as a general inhibitor of anoikis".

(7) Comment. Conclusion: "There correlation between CEA levels and survival." – This sentence is incomplete, please correct it.

Response: We deeply appreciate your suggestions. We have corrected this sentence to "High pre-LR and post-LR serum CEA levels were significantly correlated with a poor prognosis in CRCLM patients".

(8) Comment. Last sentence of the text: "Therefore, based on the results of this study, high preoperative or postoperative serum CEA levels were correlated with poor prognosis, especially poor OS, in CRCLM patients who have received LR." – "Therefore" should be omitted here.

Response: We are much obliged to you for your suggestions. In the text, we have omitted "Therefore" here. In conjunction with recommendation 7, we revised the conclusion as "High pre-LR and post-LR serum CEA levels were significantly correlated with a poor prognosis in CRCLM patients".

(9) Comment. Reference list: Capital letters should be used in journal names (and they should be abbreviated); e.g., "World journal of gastroenterology" -> World J Gastroenterol.

Response: We deeply appreciate your suggestions. We checked and changed the descriptions of journal names in all references and used capital letters.

(10) Comment. In parts, the format of the references is not consistent with the guidelines of the journal.

Response: Thank you for your careful review. We will read the submission guidelines carefully and make changes to the format of the references in accordance with the guidelines of this journal.

(11) Comment. Figures and Tables: For the publications, the citation numbers corresponding to the reference list should be added.

Response: Many thanks for your suggestions. In Table 1, we have added the citation numbers corresponding to the reference list for the included studies.

(12) Comment. Figure 1: There should be a colon (:) after "Duplicate records removed (n=2424)".

Response: Thanks for your comments. We have added a colon (:) after "Duplicate records removed (n=2424)".

(13) Comment. Figure 2: For the readers, it should be stated why "Arru" is contained twice.

Response: We are very grateful for your suggestions. We reviewed the original article and added a note below Figure 2. In the study of Arru et al., the HR (95% CI) for CEA levels >5 ng/ml was 2.10 (1.10, 3.90), and the HR (95% CI) for CEA levels <5 ng/ml was 1.60 (0.70, 3.70).

(14) Comment. Figure 2 and Table 1: There are publications by Reddy from 2008 and 2009 in Figure 2 and Table 1, but two by Reddy from 2009 in the reference list.

Response: Thank you for your correction. We have changed the 67th reference from "2009" to "2008" after checking the information in the article.

(15) Comment. Figure 4: For the readers, it should be stated why "Kawahara" is contained twice.

Response: We are very grateful for your suggestions. We reviewed the original article and added a note below Figure 2. In the study of Kawahara al., the HR (95% CI) for CEA levels >50 ng/ml was 2.15 (0.94, 4.94), and the HR (95% CI) for CEA levels <50 ng/ml was 1.51 (0.57, 3.95).

2 Editorial Office's comments

1) Science Editor: The manuscript has been peer-reviewed, and it is ready for the first decision.

Language Quality: Grade A (Priority publishing)

Scientific Quality: Grade C (Good)

Response: Thank you for your expert review of this study and we hope this correction is recognized.

2) Company Editor-in-Chief: I recommend the manuscript to be published in the World Journal of Gastrointestinal Surgery. 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: We have used the Reference Citation Analysis (RCA) to supplement and refine the highlights of the latest cutting-edge research findings. Thank you very much for suggesting this very practical tool to us. It will be very helpful and convenient for my future research and writing, thank you again for your suggestion!