

Dear Editor(s):

We once again appreciate the reviewers for their careful reviews of our manuscript and core helpful comments to let the manuscript more and more accuracy and enhanced the scientific values. We would like to take such opportunity to re-submit this revised manuscript in accordance with their comments. The following is our point-by-point response to the reviewers.

**Reply to the comments on Manuscript NO.: 88294**

Reviewer: 1

Reviewer #1:

**Scientific Quality:** Grade D (Fair)

**Language Quality:** Grade C (A great deal of language polishing)

**Conclusion:** Major revision

**Specific Comments to Authors:** The document titled "Combining Prognostic Value of Serum CA 19-9 and Tumor Size Reduction Ratio in Patients with Pancreatic Ductal Adenocarcinoma Underwent Neoadjuvant Therapy" focuses on a medical research study. It examines the prognostic significance of serum CA 19-9 levels and tumor size changes in patients with Pancreatic Ductal Adenocarcinoma (PDAC) before and after neoadjuvant therapy (NAT). There are several studies similar to the one described in your document, indicating a notable interest in the prognostic value of serum CA19-9 and tumor size changes in patients with pancreatic ductal adenocarcinoma (PDAC) undergoing neoadjuvant therapy (NAT) (1-3). These studies indicate that the investigation of serum CA19-9 levels and tumor size reduction as prognostic factors in PDAC patients undergoing NAT is a well-explored area in medical research. Thus, the current paper has been addressed in prior publications. (1) Al Abbas AI et al. Serum CA19-9 Response to Neoadjuvant Therapy Predicts Tumor Size Reduction and Survival in Pancreatic Adenocarcinoma. Ann Surg Oncol. 2020 Jun;27(6):2007-2014 (2) Imaoka et al. Post-adjuvant chemotherapy CA19-9 levels predict prognosis in patients with pancreatic ductal adenocarcinoma: A retrospective cohort study. Pancreatology. 2016

Jul-Aug;16(4):658-64. (3) Aoki et al. (2019): Decreased serum carbohydrate antigen 19-9 levels after neoadjuvant therapy predict a better prognosis for patients with pancreatic adenocarcinoma: a multicenter case-control study of 240 patients. BMC Cancer. 2019 Mar 21;19(1):252.

**Answer:** Thank you for the comments of reviewer 1. The reviewer mentioned 3 studies similar to our paper and we will describe the difference between our study to these 3 studies. With respect to the first one (Ann Surg Oncol. 2020 Jun; 27(6): 2007–2014.), the authors focused on the relationship of serum CA19-9 with other markers of response and identify thresholds correlating to outcomes. They only used the pre-treatment serum CA19-9 to predict the tumor size reduction and patient outcomes. However, in our current study, we evaluated the significance of the serum CA 19-9 and the tumor size changing pre-and post-neoadjuvant therapy (NAT). There are some similarities between the two studies, but the overall research objectives are still different. With respect to the second one (Pancreatology. 2016 Jul-Aug;16(4):658-64.), this study examined the utility of the post-AC CA19-9 level as a prognostic marker for relapse-free survival (RFS) in resectable PDAC, which was totally different from our study that focused on the serum CA 19-9 and the tumor size changing pre-and post-neoadjuvant therapy (NAT). With respect to the third one (BMC Cancer. 2019 Mar 21;19(1):252), this study defined the prognostic significance of decreased CA19-9 levels after neoadjuvant therapy in patients with pancreatic adenocarcinoma. However, in our study, we analyzed both the serum CA 19-9 and the tumor size changing to predict the outcomes precisely. In summary, we acknowledge that these studies have similarities with our own research, as there are many studies related to serum CA 19-9, but our own research still has some innovation and clinical value.

Major revision 1 Completion rate of scheduled NAT could be worth checking.

**Answer:** Thank you for the suggestion of reviewer 1. We have added the completion of NAT in the first section of results, which described as “According to the scheduled NAT management, 87.2% (136/156) completed the NAT.”

2 The univariable analyses should be describe before multivariable analyses in the part of Efficacy and Pathologic Response.

**Answer:** Thank you for the suggestion of reviewer 1. We have added the univariable analyses outcomes in the section of Efficacy and Pathologic Response.

3 The differences from other papers should be emphasized in the discussion part. Especially, AUC of CR+TR should be focused for predictive factor after NAT. Because the AUC is moderate predictive value.

**Answer:** Thank you for the suggestions of reviewer 1. We have added the contents of comparing our study with other studies in the discussion section, moreover, we have further discussed the AUC of CR+TR to predict outcomes.

4 Deep learning model about the staging of pancreatic cancer should be described in the discussion part. (Cao K et al. Deep Learning for Fully Automated Prediction of Overall Survival in Patients Undergoing Resection for Pancreatic Cancer: A Retrospective Multicenter Study. Ann Surg. 2023 Jul 1;278(1):e68-e79.)

**Answer:** Thank you for the comments of reviewer 1. We have added this model in the section of discussion.

Minor revision P13 line15; The period ( “survival. ” ) is wrong ?

**Answer:** Thank you for the comments of reviewer 1. We have changed it.

Reviewer #2:

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

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

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:** The article deals with very interesting prognostic values, the serum CA 19-9 and the tumor size changing pre-and post-neoadjuvant therapy in pancreatic ductal adenocarcinoma. The study is well organized, the number of patients is satisfactory. My concern is why the authors have chosen to include patients with a bilirubin level of, less than 2 mg/dL, since the obstruction has already been resolved.

The statistical analysis is accurate. The results are conclusive with the primary end point.

**Answer:** Thank you for the recommendation of reviewer 2. For the patients included in this study, we reduced jaundice in patients by placing biliary stents, but there were still a few patients whose bilirubin did not decrease to normal. Therefore, we also set the value of bilirubin to more effectively enroll patients. Thank you.

In short, we appreciate the time and effort which the reviewers and editors have devoted to this manuscript, and believe our modifications in response to their comments have improved the quality of this manuscript. Please let us know if there are any more questions.

Sincerely,

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