

October 29, 2018

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 41442-Answering Reviewers.doc).

Title: Prognostic significance of perioperative serum tumor marker levels in patients with stage II/III gastric cancer treated with curative gastrectomy: a multiinstitutional dataset analysis

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Name of Journal: *World Journal of Gastrointestinal Oncology*

ESPS Manuscript NO: 41442

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated according to the instructions.

2 Revision has been made according to the suggestions of the reviewer

(1) Reviewer 03728442

- This is a well-conducted and straightforward retrospective analysis on the prognostic value of perioperative serum CEA and CA19-9 tumour markers performed in a large cohort of Asian patients with resectable gastric cancer. I would recommend only few suggestions to further improve the quality of the manuscript:

Reply) We thank the Reviewer for favorable comments.

1) I would add figures in the "Introduction" section to better convey the medical unmet needs of resected patients (e.g. the percentages of recurrence rates and overall survival).

Reply) We summarize the data on recurrence rates and survival of patients with stage II/III gastric cancer from the two pivotal phase III clinical trials and presented in the Introduction part (page 7, line 8-9) with the Supplemental Figure 1. Thank you.

2) The limitations of both CEA and CA19-9 in predicting gastric cancer patients' outcome need to be discussed, i.e. their low sensitivity and specificity.

Reply) It must be an important point and has now been discussed further in the revised manuscript (page 14, line 4-6).

3) Novel emerging biomarkers aiding in risk-stratification of patients after surgical resection should be mentioned as well (e.g. Cheong et al. Predictive test for chemotherapy response in resectable gastric cancer: a multi-cohort, retrospective analysis. *Lancet Oncol.* 2018).

Reply) We thank the Reviewer for this thoughtful suggestion. As described in the article by Cheong et al., novel biomarkers for risk-stratification of patients after surgical resection were newly introduced in the Discussion part (page 16, line 22- page 17, line 3).

4) I would be interested in knowing, if any, about ethnic differences concerning CEA and CA19-9 levels (Asian vs others). If so, please discuss this in the text.

Reply) We agree with your opinion. Some descriptions related to ethnic differences in serum tumor marker levels have now been added in the revised text (page 14, line 9-13). Based on the literatures from Western and Asian countries, serum levels and clinical significance of CEA are almost identical in both areas. CA 19-9 is not expressed in patients who lack the Lewis antigen and the proportions of Lewis negative individuals are approximately 10% both in the Caucasian and Asian population. These facts indicated that our findings may be applicable in a broad area of the world.

(2) Reviewer 03726737

- Overall, this study is well-evaluated the relationship between perioperative levels of serum tumor markers including CEA and CA 19-9 and prognosis such as overall survival (OS) and disease-free survival rates in patients with stage II/III non-metastatic gastric cancer.

Reply) Thank you so much for your encouraging comments.

1. In the previous study (Dig Surg. 2018;35(1):55-63), preoperative CEA level was an independent prognostic factor of OS, not CA 19-9 level or postoperative levels. However, current study reported that postoperative levels of CEA and CA 19-9 were independent factors of prognosis. What factor does the difference between the studies contribute?

Reply) As you can see below, the trend of hazard ratios of the perioperative CEA and CA19-9 is similar between the present and previous studies.

<The present study>

	Preoperative levels						Postoperative levels					
	Overall survival			Disease-free survival			Overall survival			Disease-free survival		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
CEA (>5 ng/ml)	2.02	1.48 – 2.73	<0.0001	1.70	1.30 – 2.20	0.0002	2.30	1.59 – 3.23	<0.0001	1.89	1.36 – 2.56	0.0002
CA19-9 (>37 IU/ml)	1.59	1.11 – 2.23	0.0125	1.76	1.32 – 2.32	0.0002	2.61	1.72 – 3.81	<0.0001	2.76	1.96 – 3.78	<0.0001

<Our previous study>

Table 3. Prognostic significance of preoperative and postoperative levels of CEA and CA19-9

	Preoperative levels						Postoperative levels					
	overall survival			disease-free survival			overall survival			disease-free survival		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
CEA (>5 ng/mL)	3.52	1.70–6.89	0.0012	2.99	1.58–5.38	0.0012	2.93	0.99–6.90	0.0506	2.73	1.04–5.93	0.0423
CA19-9 (>37 IU/mL)	2.08	0.88–4.36	0.0894	2.03	1.02–3.78	0.0456	1.81	0.68–4.04	0.2166	1.80	0.78–3.63	0.1551

HR, hazard ratio; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

We speculate that the differences were mainly from the sample size and the change in standard of the adjuvant treatments, representing the value of updating data by a modern and larger database.

2. Authors evaluated the prognostic impact of perioperative tumor markers according to adjuvant chemotherapy comparing hazard ratio (HR) for death of elevated markers. Could decrease of HR levels explain the association of adjuvant chemotherapy for the poor outcome? Is there any other statistical method for verifying this prognostic impact?

Reply) In the Figure 3B, we tried to whether the risk of mortality in patients with elevated perioperative tumor markers decreases or not by postoperative adjuvant chemotherapy. As a result, adjuvant chemotherapy was associated with decreased hazard ratios in patients with elevated CEA levels, indicating it confers some survival benefit for those patients. On the contrary, hazard risks were not reduced by adjuvant chemotherapy in patients with high postoperative CA 19-9. These findings suggested unique characteristics of CEA and CA19-9 as serum biomarkers of gastric cancer. We consulted with our biostatisticians again. After much rethinking, we decided to make the above argument with the present form of the Figure 3B. We hope for the Reviewer's kind understanding.

3 Languages and typesetting were corrected throughout the manuscript by native English speakers recommended by the WJGO journal editorial office (Nature Publishing Group Language Editing).

Thank you again for publishing our manuscript in the *World Journal of Gastrointestinal Oncology*.

Sincerely yours,

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