ANSWERING REVIEWERS

January 9, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 15420-Edited.doc).

Title: Poor Oncologic Outcomes in of Hepatocellular Carcinoma Patients with Intra-Abdominal Infection after Hepatectomy

Author: Dan-Yun Ruan, Ze-Xiao Lin, Yang Li, Nan Jiang, Xing Li, Dong-Hao Wu, Tian-Tian Wang, Jie Chen, Qu Lin, Xiang-Yuan Wu.

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

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

(1) In this study, intra-abdominal infections and NLR changes could be the risk factor for early or late recurrence?

The authors' Answer: Intrahepatic recurrences were classified into early and late recurrences. It is noteworthy that early recurrence is mainly due to intrahepatic metastasis correlated with tumor-related parameters, whereas late recurrence is mainly due to multi-centric occurrence correlated with the condition of the remnant liver. In our study, the 1-, 2-, 3-, and 5-year RFS rates were 74.5%, 60%, 56.0% and 51.0%, respectively. Most of the tumor recurrence occurred during the first two years after surgery. And delta-NLR and intra-abdominal infection were independent prognostic factors for 1y-RFS ($p=0.004$ and $p<0.001$). It suggested that delta-NLR and intra-abdominal infection were risk factors for early recurrence, which might be attributable to the immune reponse during infection and promote tumorigenesis.

(2) The authors indicated that intra-abdominal infection had significant correlation with hepatic cirrhosis, concomitant splenectomy, and vascular invasion. Does delta-NLR have correlation with any clinicopathological factors?

The authors' Answer: We followed the suggestion and added it to table 2. However, the result showed no significant correlation between delta-NLR and any clinicopathological factors.

(3) Definition of "infection" is not clear. Diagnosis of "infection" is difficult except blood culture, because isolation of microorganism does not always mean pathogenic infection, that depends on the bacterial species, including normal bacterial flora. This manuscript does not include what kind of bacteria was separated, so the justification of "Intra-Abdominal infection" cannot be evaluated.

The authors' Answer: I agree with your comments. The positive incidence of bacterial culture is relatively low after the usage of antibiotics, so it's difficult to make an etiology diagnosis. In the study, the infectious complications was defined mainly based on a clinical diagnosis, including the symptoms with clinical/physical examination signs (pyrexia, abdominal pain, abdominal tenderness, etc.), raised inflammatory markers, positive fluid/blood cultures, radiologic signs and requirement for antibiotics or further intervention.

(4) Why choose the NLR on the 7th day after surgery?

The authors' Answer: We would like to observe the dynamic change of NLR, which might reflect the

dynamic change of balance between host inflammatory response and immune response. In this study, the peak time of postoperative infection was around 1-2 weeks and a routine blood test was taken one week after surgery in our institution. For the reason of that, we choose the NLR on the 7th day after surgery as the postoperative NLR value.

(5) Intra-abdominal infection occurs in the early or late period after surgery? The author should show the time of intra-abdominal infection, for example, in the early three months after surgery or....

The authors' Answer: The intra-abdominal infection occurs in the early period after surgery, among 1-2 weeks after surgery. We added it in the article.

(6) From Table 2, the author considered multiple infection as intra-abdominal infection. From Table 1, multiple infection had 7 patients, accounting for 28% (7/25) of Intra-abdominal infection. So the conclusion, intra-abdominal infection adversely affected oncologic outcomes, is not reliable.

The authors' Answer: In the 7 patients with multiple sits of infection, 6 of them were suffered intra-abdominal infection and pulmonary infection, one was intra-abdominal infection and wound infection. We analyzed the patients with pulmonary infection included those with multiple infection, and found there were no significant difference between pulmonary infection and non-pulmonary infection group in RFS or OS. Therefore, we inferred that intra-abdominal infection affected the outcomes. We agree the influence of multiple sites infection should to be validated in larger studies.

(7) In this sentence" In further analysis, there were significantly increased incidences of postoperative intra-abdominal infection in patients with hepatic cirrhosis (p=0.028), concomitant splenectomy (p=0.007) and vascular invasion (p=0.026) (Table 2)", the author should analyze risk factors of intra-abdominal infection in the Multivariate analysis, not only in the Univariate analysis.

The authors' Answer: We followed the suggestion and added the result in table 2. In multivariate analysis, intra-abdominal infection had significant correlation with hepatic cirrhosis, concomitant splenectomy, and vascular invasion. (p=0.043, p=0.116 and p=0.006, respectively)

(8) In the disscussion," Postoperative NLR change was an independent factor for tumor recurrence." From Table 3, we can conclude that postoperative NLR change was an independent factor predictor for recurrence free survival (RFS) not the tumor recurrence.

The authors' Answer: We apologize for the inaccurate expression we've made in the manuscript and it has been checked and corrected.

(9) The intro-abdominal infection mentioned in the article is a little higher in those patients with larger tumor diameters and vascular invasion. Should this influence the results?

The authors' Answer: In the correlation analysis, there were significantly increased incidences of postoperative intra-abdominal infection in patients with hepatic cirrhosis, concomitant splenectomy and vascular invasion. In the multivariate Cox regression analysis, postoperative intra-abdominal infection was an independent predictive factor for RFS, whereas tumor size and vascular invasion didn't show significance. The influence of tumor invasion needs to be confirmed in larger studies.

(10) Could the author mention the type and the main cause of the intro-abdminal infection?

The authors' Answer: In the present study, the type of intra-abdominal infection included subphrenic infection, peritonitis, infected intra-abdominal fluid collection, infectious enteritis and bile leakage. The main causes were subphrenic infection and bile leakage.

3 References and typesetting were corrected

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

Sincerely yours,

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