January 16, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ESPS-14390-review.doc).

Title: Correlation between metastatic lymph node ratio and prognosis in patients with distal cholangiocarcinoma

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 14390

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) Please explain why nearly 40% of the patients were excluded?

Answer: We have explained the reason of nearly 40% of the excluded patients in the manuscript.

(2) In the result section, "tumor differentiation" was found to affect survival. However, the paper does not offer a definition for the term. In the method section of the paper, please define "tumor differentiation" and how it was calculated?

Answer: We have defined "tumor differentiation" and how it was calculated in the method section of the paper.

(3) Lymph node metastasis has to be better defined in the method section of the paper. Was it local lymph nodes or distant lymph nodes or both?

Answer: We have defined lymph node metastasis in the method section of the paper. Both.

(4) In the method section of the paper, please explain how the cutoff points of 0.2 and 0.4 were chosen for MLNR?

Answer: We have explained how the cutoff points of 0.2 and 0.5 chosen for MLNR in the manuscript.

(5) What exactly are distal cholangiocarcinomas (CCA) for the authors ? It is more common to talk about intra- and extrahepatic CCA?

Answer: Extrahepatic CCA.

(6) Lymph nodes are very rare in CCA, normally not more than 5. The authors should further discuss this point?

Answer: We have discussed it in the manuscript.

(7) The introduction is very short and missing general information about CCA, terminology, histology, etc?

Answer: We have added the general information about CCA in the introduction of the paper.

(8) How was exactly the calculation of MLNR performed ? What does 0.2 or >0.5 stand for?

Answer: MLNR was calculated by the ratio of metastatic/dissected lymph nodes.

(9) There are no information about underlying liver disease or co-diseases, which definitely will influence survival?

Answer: The subjects enrolled in our study had no liver disease or co-diseases, which had been added to the manuscript.

(10) The are two scores worldwide used for the staging of lymphnodes for CCA. 1) TNM, 2) Consensus classification from the European Hepato-Pancreato- Biliary Association: Both scores have to be discussed in the manuscript?

Answer: The staging of lymphnodes for CCA in our study was defined according with TNM. Another criterion was not used.

(11) Fig. 2/3 better change month to years. The authors should also show the patients at risk for the investigated time-points?

Answer: We have changed month to years in Fig. 2/3, and we have showed the patients at risk for the investigated time-points.

(12) The authors reached a similar findings were already published in other tumor type. The authors stated there is no study has Explored the correlation MLNR Between Patients and prognosis in DCC?

Answer: We have changed the statement into "there are few studies about the correlation between MLNR and prognosis in ECC patients".

(13) It is surprising that the third author (Xu Che) designed the research, analyzed the data, and wrote the paper. Normally the first author takes a main part of responsibility of publication (designe, analysis, and reporting of results)?

Answer: We have corrected the author contribution.

(14) Running title - it does not reflect the content of the article?

Answer: We have corrected running title for "prognostic factors in patients with extrahepatic cholangiocarcinoma".

(15) The pages must be numbered?

Answer: We have numbered the pages.

(16) As the preoperative investigation only abdominal CT / MRI / ultrasound and determination of serum tumor markers are included, therefore the definition of tumor stage is not complete?

Answer: Histological specimens have been examined postoperatively by pathologists in our hospital.

(17) In Materials and methods part of the manuscript there is no enough explanation why the MLNR groups (0, 0-0.2, 0.2-0.5, and> 0.5) has been chosen by the Authors. Although some notes can be found in the Discussion part of the manuscript as well, but the explanation must be included in the Materials and Methods section?

Answer: We have explained in the Materials and Methods section.

(18) There is a few redundant part in the manuscript, which is unnecessary and should be avoided. E.g In the **Materials and Methods** section ("Data analysis") lists the analyzed clinicopathological data s (age, sex, operative duration, etc.) These text provided again in the **Results section** ("Results of Univariate analysis")?

Answer: We have corrected the redundant parts in the manuscript.

(19) metastatic lymph node ratio was abbreviated as MLMR, RLNM instead of MLNR, ….

Kaplan-Meirer…, naïve?

Answer: We have corrected the abbreviation.

(20) "Long-term survival" would be more accurate long-term patient survival, etc?

Answer: Yes, we have corrected.

(21) Table 2: shows that patient survival is better who has perineural invasion ("Yes" line), than those who did not have ("No" line). Is it a typo? If not, please explain how these results can be explained?

Answer: Yes, it was a typo, and we have corrected.

(22) Fig. 1-2: This figure difficult to understand at least printed in black and white?

Answer: We have corrected the Fig. 1-2 into colorful figure and saved it as tif format.

(23) References: Several recent publications appeared about the distal cholangiocarcinoma and its prognostic factors, upgrading is necessary?

Answer: We have upgraded the recent publications.

(24) One wonders what happened with the remaining patients and why these were excluded?

Answer: We have explained it in the manuscript.

(25) The authors point at the relevance of improved surgery and also skilled pathology in order to get a sufficient number of lymph nodes to examine. Was a uniform and standardized pathological protocol without any changes over time used during the whole period?

Answer: Yes, the histopathological diagnosis and staging were based on the 6th edition of the American Joint Committee on Cancer (AJCC) cancer staging system.

(26) Did the number of surgically removed lymph nodes change over time in parallel with improved surgical skills?

Answer: Yes, the number of surgically removed lymph nodes changed over time in parallel with improved surgical skills.

(27) With metastatic lymph node ratio demonstrated to be an independent diagnostic factor, one wonders what this information would change concerning management and strategy decisions?

Answer: We have added related information in the manuscript.

(28) Similar correlations had been demonstrated in both intrahepatic and extrahepatic cholangiocellular carcinomas and for pancreatic ductal adenocarcinomas. The authors actually themselves point at the work by Kawai et al (ref no. 13) demonstrating the metastatic lymph node ratio to be an independent prognostic factor for bile duct carcinomas. By this, the added novelty value is limited?

Answer: The differences between our study and Kawai's were as followed: a. there were more subjects in our study (78 cases) than in Kawai's (62 cases); b. the population of subject was different; c. the cut-off points of MLNR was more rigorous in our study (0.2 and 0.5) than in Kawai's (only 0.2).

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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