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Editors-in-Chief *World Journal of Gastroenterology*

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Dear Profs. Garcia-Olmo, Strom, and Tarnawski,

We would like to thank you and the reviewers for the positive remarks concerning our article. The manuscript was modified according to the reviewer comments. Changes made in the manuscript are highlighted in yellow in the new version. Moreover, you find hereunder a point-by-point reply to the reviewer comments.

Reviewer 1:

The authors have investigated 68 patients who underwent hepatectomy for liver echinococcosis and concluded that preoperative serum albumin level is a predictor for liver recurrence. Because of the rare cases, their study is unique. However, there are many queries in this study, which should be responded in the revised manuscript. The queries are shown as the followings:

1. Because of the rare cases, only 9 cases had recurrent AE, thus, comparison of small number of recurrent cases and non-current cases may be not so clinically important in spite of statistically significant higher recurrence in patients with low serum albumin level and histological positive resection margin (independent predictor). Therefore, the authors should indicate the liver resection strategy for AE in the "Patients and Methods" section.

We thank the reviewer for this comment. All patients with liver AE or high suspicion of AE independently of the lesion size were candidates for hepatectomy. Anatomical resections were performed. Contra-indications to surgery were Child C cirrhosis, comorbidities precluding general anesthesia, or estimated future remnant liver <30% of total liver volume after portal vein embolization. The strategy of liver resection was clarified in the Materials and Methods (page 7).

Who performed liver resection during the 24-year study period?

During the study period, only 3 senior surgeons specialized in alveolar echinococcosis performed the liver resections. This was added in the manuscript (page 8).

Because "serum albumin level" is also a factor of Child-Pugh classification. Surgeons may be not select patients with low albumin level for hepatectomy. Thus, the authors' conclusion may be not possible if surgeons do not select patients with hypoalbuminemia for operation.

Hypoalbuminemia was not a contra-indication to surgery *per se*. Only Child-Pugh C stage was a contra-indication to resection, but no patient during the study period presented with AE and Child-Pugh C cirrhosis.

Moreover, are there any resection strategy change between the early and the late period?

No strategy change happened during the study period. All patients with confirmed liver AE or highly suspicious lesions underwent anatomical liver resections. This was clarified in the Materials and Methods (page 7).

When was the major or minor hepatectomy done?

Between 1992 and 2003, major hepatectomies were performed in 12 patients and minor in 10. Between 2004 and 2015, major hepatectomies were done in 27 patients and minor in 19 patients. This was added in the manuscript (page 10).

Since this is a retrospective study and the study period is very long (24 year), there may be some changes in surgery in this period.

No changes in surgical strategy happened. Anatomic resections were systematically performed. Only a program of Enhanced Recovery after Surgery was implemented in liver surgery in 2013 in our division. Of course, experience and surgical expertise have probably grown during the years. This point was added in the limitations (page 14).

2. In table 1, univariate analysis should show the actual disease-free (DF)

survival data (for example, median DF time, or 1,3,5-year DF survival rate) with a "P-value" instead of the presenting HR, and 95% CI. It will be more convenient for readers to understand the actual results of each variable.

This is a good point. To be more convenient for readers and not to overload table 1, these data were added in a table 2 (page 24).

In addition, is there any definition for "portal vein invasion" of AE in table 1?

The definition of portal vein invasion was specified (pages 23 and 25).

3. Using ROC curve, the authors proposed that serum albumin level 37.5 g/l is a good cut-off value, the sensitivity 94.5% and specificity 75%. However, the authors should also provide the "predictive value of positive", "predictive value of negative " and "accuracy" of the study.

That is a good point. Positive predictive value was 60%, negative predictive value 96%, and likelihood ratio 3.7. Positive and negative predictive values were added in the manuscript as well as the likelihood ratio (page 11).

4. How about "overall survival rate" of AE with or without recurrence?

Thank you for your comment. Overall survival rate was 81 months *vs.* 69 months (p=0.932) for patients with and without recurrence, respectively. These data were clarified in the text (page 10).

How about the further managements for AE patients with recurrence? Why OS in recurrent cases was longer than that in non-recurrent cases.

Precisions were made regarding the management of patients with recurrence (pages 10-11). Four patients underwent repeat hepatectomy, 1 biliodigestive bypass, 1 thoracic wedge resection, and 2 long-term albendazole treatment. OS was 81 months in patients with recurrence and 69 months in patients without recurrence, but they were not significantly different (p=0.932). Therefore one cannot conclude that one was longer than the other.

5. In survival rate calculation, the operative death should be not included.

The perioperative death was excluded from the survival rate calculation. Figure 3 was therefore changed (page 22).

Moreover, in the recent studies of liver resection. It would be better to use 90-day mortality.

Ninety-day mortality (1/68=1.5%) was added (page 10). It was similar to the 30-day mortality.

6. The authors should explain the possible mechanism of preoperative lower albumin level had higher recurrent rate.

Preoperative lower albumin level could be correlated to the inflammation intensity caused by liver alveolar echinococcosis. It could also reflect the intrahepatic dissemination of *Echinococcus multilocularis* altering the albumin synthesis. These possible suggested mechanisms were added in the discussion (page 13).

Moreover, as a small case number to be an independent predictor of early AE recurrence, I think that change as "Preoperative hypoalbuminemia is associated with early recurrence of AE after hepatectomy".

Taking into account the small number of patients, the term "associated" was now used in the manuscript (pages 5, 12).

In addition, if surgeons supply "albumin" to patients with low albumin level before operation, how do the authors think using this policy?

This is a relevant and difficult question, as no data exist on this subject. In this cohort, no patients received IV albumin preoperatively. As albumin level is considered to reflect the inflammatory state of the patients infected by *Echinococcus multilocularis,* if surgeons use albumin preoperatively the albumin level that should be taken into consideration for risk of recurrence would be the one before supplementation. Moreover, it is not sure if IV albumin can stably increase albuminemia. No data exist on albumin supplementation and alveolar echinococcosis recurrence in case of preoperative hypoalbuminemia. Further studies would need to clarify that point. This problematic was added to the discussion (page 13).

Reviewer 2:

This is a single-center retrospective study of 68 patients who underwent liver resection for alveolar echinococcosis (AE). The authors found that preoperative albumin level is a significant risk factor for recurrence of AE. This is an interesting result from highly experienced European center for AE. I have only several minor comments.

1. The running title "recurrent alveolar echinococcosis" should be modified.

It has been modified as follows: "Hypoalbuminemia and recurrent alveolar echinococcosis" (page 1).

2. How about hemoglobin or serum bilirubin level, if available?

Hemoglobin and bilirubin levels were added in tables 1 and 2 but were not significant in univariable analysis (pages 23-24).

3. Which version of GraphPad Prism and SPSS were used?

GraphPad Prism 5.0 and SPSS 19.0 for Mac OS X were used. This was specified in the Materials and Methods (page 9).

4. In introduction, "Potential predictive blood markers should be easy to measure and interpret. This is why more sophisticated inflammatory proteins, such as IL-6 or lactates, were not taken into account in this study." may not be correct. It should be removed.

The first statement was modified, and the second sentence was removed (page 6).

5. In discussion, the authors frequently compared hepatocellular carcinoma with AE, however, I think the two diseases are different. Comparing with the results of cholangiocarcinoma patients who do not have underlying liver disease may be more appropriate.

That is a good point. Comparisons with cholangiocarcinoma were added in the discussion (pages 12 and 18).

6. How frequently were the patients followed up postoperatively after the one-month check-up?

They were seen for a clinical encounter at 6 months and 1 year after the operation by the surgeon. Moreover, patients had regular (monthly) appointments with the infectiologist for the follow-up of albendazole blood levels and regular serologies. In case of clinical recurrence suspicion or positive serologies, a complementary imaging (CT/MRI) was performed. The follow-up was clarified in the Materials and Methods (page 8).

And please explain in detail how albumin can help guide the postoperative follow-up of AE in discussion.

This was explained more in details in the discussion (e.g., closer clinical follow-up, more frequent serologies or radiological examinations in case of hypoalbuminemia) (page 12).

We hope that the changes made in our manuscript will allow its publication in your Journal.

Yours sincerely,

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