

December 17, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: MainDocument\_Rev.doc).

**Title:** Hepatobiliary Complications of Alveolar Echinococcosis: A Long-Term Follow-up Study

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**Name of Journal:** *World Journal of Gastroenterology*

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The authors thank the editors and reviewers for their valuable comments. Based on their suggestions we performed revisions and critically discuss all the points raised. The appropriate changes are now included in the text and are given below. We believe that these have considerably strengthened the manuscript. The changes are addressed in a point-by-point fashion.

**Reviewer 1 (No. 2542637)**

1. Major Weaknesses: On the bases of MEDLINE search, it can be concluded that several published studies (see below) have similar design and practically the same conclusions:
  - a. Ozturk G, Polat KY, Yildirgan MI, Aydinli B, Atamanalp SS, Aydin U. Endoscopic retrograde cholangiopancreatography in hepatic alveolar echinococcosis. *J Gastroenterol Hepatol.* 2009 Aug;24(8):1365-9. doi: 10.1111/j.1440-1746.2009.05877.x.
  - b. Akaydin M, Eroozen F, Ersoy YE, Birol S, Kaplan R. Treatment of hepatic hydatid disease complications using endoscopic retrograde cholangiopancreatography procedures. *Can J Surg.* 2012 Aug;55(4):244-8. doi: 10.1503/cjs.036010.
  - c. Giouleme O, Nikolaidis N, Zezos P, Budas K, Katsinelos P, Vasiliadis T, Eugenidis N. Treatment of complications of hepatic hydatid disease by ERCP. *Gastrointest Endosc.* 2001 Oct;54(4):508-10.
  - d. Sharma BC, Reddy RS, Garg V. Endoscopic management of hepatic hydatid cyst with biliary communication. *Dig Endosc.* 2012 Jul;24(4):267-70. doi: 10.1111/j.1443-1661.2011.01225.x. Epub 2011 Dec 29.
  - e. Goumas K, Poulou A, Dandakis D, Tyrmpas I, Georgouli A, Sgourakis G, Soutos D, Karaliotas K. Role of endoscopic intervention in biliary complications of hepatic hydatid cyst disease. *Scand J Gastroenterol.* 2007 Sep;42(9):1113-9.
  - f. Tekant Y, Bilge O, Acarli K, Alper A, Emre A, Ario?ul O. Endoscopic sphincterotomy in the treatment of postoperative biliary fistulas of hepatic hydatid disease. *Surg Endosc.* 1996 Sep;10(9):909-11.

Moreover, a few months ago, an article had been published in this journal [Frei P, Misselwitz B, Prakash MK, Schoepfer AM, Prinz Vavricka BM, Müllhaupt B, Fried M, Lehmann K, Ammann RW, Vavricka SR. Late biliary complications in human alveolar echinococcosis are associated with high mortality. World J Gastroenterol 2014; 20: 5881-5888] with a very similar design, but with much larger series of patients. Authors specified that “Frei et al. has investigated survival following onset of hepatobiliary complications. They report a survival of only three years following onset of complications.... By contrast, data of the present study show an average survival of 8.8 years following onset of complications” However, they did not provide convincing evidence that this difference justifies the publication of another article with a similar design and conclusions on the same subject in the same journal.

**We cannot agree with the above conclusions and criticisms of Reviewer 1 regarding our study. The studies he cites (b-f) deal exclusively with complications of cystic echinococcosis rather than with alveolar echinococcosis (AE) as investigated in our study. Similarly, he cites studies by Öztürk (n = 13) and Frei (n = 26), both of which reported on significantly fewer patients with complications. Our collective (n = 357) is also significantly larger than those of either Frei (n = 148) or Öztürk (n = 13). To our knowledge, our collective, with follow-up of 35 patients with biliary complications of AE, is the largest reported to date.**

2. In discussion section, authors did not specify the limitations of the study. However, this is a retrospective design without comparison group and with relatively small series of patients who were treated over a large span of time. Also, this section should start with the main relevant facts of the current study.

**As recommended by the Reviewer, a passage discussing the retrospective study design as a limiting factor has been added to the Discussion. As mentioned above, our collective remains the largest collective with AE followed to date.**

3. The first 2 paragraphs (264 words) of the discussion section belong to the Introduction. **As suggested by the reviewer, the first paragraphs of the discussion have been deleted and partially inserted into the introduction**

#### **Reviewer 2 (No. 2720326)**

1. General remarks: The paper compares patients with resectable and non-resectable AE. Obviously, about one third of the patients had resectable AE (n=132; 37%), since 63% (n=225) were declared to have non-resectable lesions. If the foci have been successfully resected, one wouldn't expect the same range of hepatobiliary complications than in patients with non-resectable AE where the causative agent persists. Therefore, these two groups should not be compared. Instead, a clear distinction is recommended between patients who underwent curative surgery and those who didn't (compare Fig. 2, for example). Not surprisingly, those patients who had resectable AE were not in need for endoscopic intervention after receiving curative surgery. You name ERCP a

treatment method, but this is only true in a broader sense. Actually, it's a diagnostic method ('-graphy') that becomes a treatment method when combined with stent placement, for instance. You should clearly specify this fact.

**We agree with the Reviewer that ERCP is primarily a diagnostic imaging method. However, because over 80% of patients underwent an intervention, we believe that, in this context, ERCP may justifiably be considered a diagnostic method. The corresponding passage in the Results section has been modified to more precisely reflect this.**

2. Summary: Results: ERCP: 29, MRCP: 5 patients. This is 34 in sum. What about the 35th patient? Since you don't mention the other variants here (ERCP w/o stent placement, PTCd), it seems that one case is missing.)

**We agree with the Reviewer that the current description of the methods is difficult to understand. Since a patient may have received more than one intervention, it is not possible to count these numbers together. The frequency is based on all performed interventions. The paragraph has been re-formulated to avoid this misunderstanding.**

3. Introduction: You state the liver to be the first organ affected by metacestode development. Actually, this is mostly, but not always the site of primary infestation. Moreover, not only infiltration of closely located organs, but also distant metastatic spread (especially to the lungs) may occur.

**We cannot agree with the Reviewer on this point. Our own observations and experience, supported by data from the French research group of Dominique Vuitton, identify the liver as the primary manifestation site in practically all cases of alveolar echinococcosis. Only in the rarest cases can other organs, such as the spleen, brain, heart or bones be identified as the primary site of infection with *E. multilocularis*. Infestation of the lungs is extremely rare. See Brunetti E, Kern P, Vuitton DA; Writing Panel for the WHO-IWGE. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. *Acta Trop.* 2010 Apr;114(1):1-16.**

4. Results: Please indicate how many of the 35 patients have undergone successful resection of the AE lesion and how many interventions were needed in these cases compared to those who had non-resectable AE.

**As presented in the Results section, a total of 14 patients underwent surgery, 12 of these before, two after, the intervention.**

5. Results: 5th section, 2nd sentence: word order needs correction.

**We agree with the reviewer that the sentence is not correct. The sentence has been corrected.**

6. Discussion: 'This was significantly more rapid than the average ...' – Don't use this statistic term if your conclusion is not based on statistical analyses.  
**As suggested by the reviewer the word "significantly" has been deleted from the sentence.**
7. 'Only the subgroup of ten patients ... showed an elevated complication rate of 28.7%: ...' – In the results part, you write about 28.6% (not 28.7) of patients showing complications after ERCP with stent placement, but these cases are included in a number of 12 people in which complications occurred within one week. In the results section, you didn't indicate that they did not resolve within one week.  
**We agree with the Reviewer that the formulation in this section is not sufficiently precise. The passage in the Results section has been correspondingly revised.**
8. 'Frei et al. also report the onset of hepatobiliary complications following on average ...' – following what?  
**As correctly noticed by the Reviewer, the above mentioned sentence is incomplete. This sentence has been completed as followed: "On average, Frei et al. also report the onset of hepatobiliary complications 15.0 years following first diagnosis of AE [18] compared with an average 3.7 years in the present study. "**
9. In the last section, you say that endoscopic interventional methods can be an alternative to surgery, but you don't explain what kind of surgery you mean. You can't mean curative resection of the AE lesion, of course, but you have not explained possible surgical treatment options in cases of non-resectable AE with hepatobiliary complications before, nor have you mentioned the complication rates associated with these surgical treatment options.  
**We agree with the Reviewer that the conclusions drawn in the last section do not apply. This passage in the Discussion has been correspondingly revised.**
10. Fig. 1: The values in the boxes in the upper left and lower right corner are not used mathematically correct, e. g. '< 5 years' is a part of '< 10 years'.  
**As correctly noticed by the Reviewer the values in the boxes have been corrected**
11. Fig. 2: In the box in the lower left the sum is 8, so 1 case is missing.  
**We agree with the Reviewer that, in the box, one case is missing. The mistake has been corrected.**
12. Besides these regards to the content, there is need for some improvement of the language, as follows:
  - a. General remark: You often use 'an average', which must be either 'on average' or 'on an average'.
  - b. Running title: '... of Alveolar Echinococcosis'
  - c. Summary: Aim: 'Objective of the study was to study ...'

- d. Methods: The last sentence is incomplete.
- e. Introduction: ' Worldwide, the parasite's range is limited ...' – A parasite is not a person, so 'the range of the parasite' should be used '... is its tumor-like growth, which may infiltrate ...' – Growth cannot infiltrate (but may lead to infiltration). Last sentence of the first section: 'Only in two of

**As suggested the phrases have been corrected.**

**Reviewer 3 (No. 2729184)**

1. The authors did not find statistically significant difference in the rate of surgery between the groups with and without hepatobiliary complications ( $p > 0.05$ ). In the group of patients ( $n = 12$ ) who underwent surgery, was the rate of performing ERCP, PTCD or MRCP statistically higher in comparison to patients who did not receive surgical resection? In other words, do surgically treated patients in the presented study suffer more complications and need more frequently interventions and diagnostics?  
**As suggested by the Reviewer the above mentioned question has been analyzed. When comparing the two groups, a significant difference regarding the complication rate could not be shown ( $p = 0.6990$ ).**
2. The Authors report that the average age at time of death was 75.6 years (range 18-91 years), while the average time from onset of hepatobiliary complications to death was 7.2 years. Is there a statistical significance in the cumulative survival probability for patients who receive interventions in comparison to patients who did not?  
**The assessment of vital status was only done for patients with complications. Therefore cumulative survival probability cannot calculated.**

Sincerely yours,

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