Author’s response to reviews

Title: Portal vein thrombosis in liver cirrhosis: Incidence, management, and outcome

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Author’s response to reviews:

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Dr. King-Wah Chiu

BMC Gastroenterology
Thank you for your e-mail of May 18, 2017. The original manuscript was re-written, taking into consideration the comments raised by the editor and reviewer.

Based on your instructions, we logged into the Author Center website and uploaded the file of the revised manuscript (including the Tables) and figures. We also pasted the point-by-point response to the comments raised by the reviewer and Editor in the appropriate location on the site. To allow easy access to our response to the comments raised the reviewer, we also include a copy of our response in this letter.

We take this opportunity to express our gratitude to the reviewer and the Editor for their constructive and useful remarks. Their comments allowed us to identify areas in our manuscript that needed modification and clarification.

I hope that the revised manuscript is now acceptable for publication in the BMC Gastroenterology.

Sincerely yours,

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Response to the comments of Reviewer 1 (Dr. Quirino Lai)

We thank the editor and reviewers for evaluating our manuscript. The following text describes our responses to the comments. All line numbers mentioned in each response to each comment refer to the small-size numbers that appear on the left margin of the text of the revised manuscript.

This is an interesting retrospective study from Japan investigating the role of danaparoid sodium for the treated of PVT in cirrhotic patients. The population is relatively small (n=90) but the results are interesting and relatively innovative.

Major comment:

1) It is not clear how the Authors constructed their multivariable model. I think it is correct to report that this statistical method has been used into the appropriate "Statistical Analysis" section. Moreover, the Authors reported in Table 3 that the model was constructed using patient survival as dependent variable. Such a datum is coherent with the results (age and HCC as risk factors and patent PV as protective factor). However it is not clear when the patency was defined, as the Authors wrote in the definition of Table 3: "Determinants of survival of patients with liver cirrhosis and portal vein thrombosis after initial treatment, repeat treatment and maintenance therapy." Which is the exact timing when they categorized the PV patency for doing this analysis?

In Page 13, line 238-240, the Authors report the erroneous sentence that "Multivariate analysis identified HCC (HR 3.2426, P=0.0038), age (>65 years; HR2.9734, P=0.0178), and main portal vein patency (HR 0.4149, P=0.0205) as significant independent risk factors of PVT". Such a statement is in conflict with Table 3, in which, more accordingly, the dependent variable is patient death and not PVT. In fact, all the patients investigated in the present series had a PVT. Moreover, why the Authors did not investigate the risk factors for definitive PVT treatment failure? I suppose such an analysis is surely more intriguing respect to the risk factors for patient death.
Response: We apologize for the inadequate explanation. I was considering factors contributing to the survival of patients with portal vein thrombosis. Naturally, there are various stages in liver cancer, and it is natural that presence or absence of merger of liver cancer influences the prognosis. Therefore I would like to delete this sentence (Page 13, line 239-244) and Table 3. I would like to further investigate the successful treatment for portal vein thrombosis treatment. It is a subject for future analysis.

Minor comments:

1) English style reevaluation is needed.

Response: I checked with an English proofreading company.

2) Page 8, lines 131-134: I suppose the following sentence presents an error: "We divided the patients into two groups; patients of the acute type (n=27) developed cirrhosis within one month after hepatectomy (16 cases) or splenectomy (11 cases), while those of the chronic type (n=63) comprised all other patients."

I suppose the Authors intended that 27 patients developed PVT after hepatectomy or splenectomy.

Response: We apologize for the inadequate explanation. We intended as you pointed out. We revised the text (Page 8, lines 134-138).

3) Page 26, Table 1. I suggest to report in a more homogeneous way the reported numbers, using always the same digit of numbers after the comma. Also all the percentages need to be reported homogeneously. Such a coherence should be extended to the entire text.

Response: We apologize for the inadequate explanation. We intended as you pointed out. We revised the text (Page 26, Table 1).
We thank the editor and reviewers for evaluating our manuscript. The following text describes our responses to the comments. All line numbers mentioned in each response to each comment refer to the small-size numbers that appear on the left margin of the text of the revised manuscript.

Thanks to authors for presenting interesting article to BMC gastroenterology. Several studies have implicated the usefulness of danaparoid sodium and/or antithrombin III, in the treatment of portal vein thrombosis in patients with liver cirrhosis. Although the subject of this study is interesting and important, the methodology has a few pitfalls. As authors described in the discussion section, this study used retrospective cohort format and I think selection bias cannot be excluded. The introduction part of manuscript is a little long. All patient have relatively low Child-Pugh score, compared to the patients in real life.

- What do you mean with "acute cirrhosis" and how did you diagnose it? Acute type cirrhosis? (8-130) "We divided the patients into two groups; patients of the acute type (n=27) developed cirrhosis within one month after hepatectomy (16 cases) or splenectomy (11 cases), while those of the chronic type (n=63) comprised all other patients".

Response: We apologize for the inadequate explanation. As pointed out, we defined PVT within one month after hepatectomy or splenectomy as “Acute type”. Because CECT is often taken early postoperatively. We revised the text (Page 8, lines 134-138).

- You mean "the risk of progression of PVT"? (14-245) "The results of this study showed that anticoagulation with DS is safe and effective treatment, significantly reducing the risk of PVT and liver decompensation"

Response: We apologize for the inadequate explanation. We intended as you pointed out. We revised the text (Page 14, lines 249).

- Which study's results? (14-260) and, in which kind of patients?

"Our results showed cumulative incidence of PVT of 4.6%, 8.2%, and 10.7% at 1, 3, and 5 years, respectively, suggesting high risk of PVT even at baseline and that such risk remains stable over time".

Response: We apologize for the inadequate explanation. We deletes this sentence because it is an inaccurate description.
- Did the patients have any other reason for PVT other than cirrhosis, such as hypercoagulopathy? In addition, was there any relationship between treatment responses?

Response: We apologize for the inadequate explanation. PVT was occurs by not only reduced flow velocity but also procoagulant imbalance and vessel-wall abnormalities (Virchow's triad) are mechanistic factors in this complication, and it is related to the therapeutic response. In this study, we have not examined coagulation in detail. So we emphasized that further studies should be performed.

- What is the role of spontaneous portal vein recanalization in your study?

Response: We apologize for the inadequate explanation. By preventing portal vein occlusion, we believe that it is possible to maintain portal blood flow, make treatment possible when hepatocellular carcinoma develops, and improve prognosis.

- What is the final and new message of this study? It must be clearer in the conclusion part of manuscript.

Response: We apologize for the inadequate explanation. Warfarin following danaparoid sodium for the treatment of PVT in patients with liver cirrhosis was safe and effective. An early diagnosis of PVT along with the evaluation of the volume of PVT on CT and an early intervention would contribute to the higher efficacy of the treatment. Prevention of PVT or successful recanalization of a previously thrombosed portal vein can potentially improve survival of such patients. We revised the text (Page 3, line 68-72, Page 17, lines 332-338).