Milan, 9th October , 2015

Dear Editor,

We have the pleasure to resubmit for your consideration a revised version of our manuscript **Therapeutic and clinical aspects of portal vein thrombosis in patients with cirrhosis** which has been edited in accordance with the criticisms/suggestions raised by the reviewers. All changes have been highlighted in the new version of the main text.

At this point, we would like to thank the reviewers for their constructive observations that undoubtedly have helped us to improve the quality of this manuscript.

We hope to have satisfactorily addressed the majority of the issues raised. We would be delighted if you find this revised version of the manuscript now suitable for publication in World Journal of Hepatology.

Sincerely yours,

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A point by point response is following listed. The original comments of the reviewers are reported in italics.

Rewiever 1

Thanks to the reviewer for his/her fruitful comments.

1. *Although the pathophysiology of PVT in cirrhosis is mentioned in the introduction section, we suggest authors make it more structured and comprehensive. Besides, the risk factors of PVT in cirrhosis should be added in the literature.*

We have opportunely added a specific paragraph on this topic in the new version of the manuscript. Thank you for the suggestion.

2. *The authors could discuss more about the effects and impact of PVT on survival, disease progression, and complication in cirrhosis and liver transplantation.*

This is a very important observation. Accordingly, we have reported the most important and consistent data on this hot topic and added a new paragraph in this version of the manuscript.

3. *Since the pathophysiology of PVT in cirrhosis can be divided into acute and chronic phase, is there any difference of management between these two phases ?*

This is an interesting point, however the pathophysiological classification of PVT in acute and chronic has a correspondence to the clinical presentation of the patients mainly in the context of extrahepatic portal vein obstruction in non-cirrhotic patients and not in cirrhosis (Plessier et al., J Hepatol 2012). Indeed, in this last clinical setting, the detection of PVT is generally incidental during the surveillance for HCC and the data on “acute” PVT in cirrhosis have not been systematically collected. For these reasons, we hope the reviewer considers opportune our final decision to do not discuss this issue more extensively in the new version of the manuscript.

4. *Because the rationale of PVT cirrhosis management is individualized, detailed data of previous studies including baseline characteristic of enrolled patients, efficacy, and safety should be offered in this review article. We suggest the authors to provide a Table to summary studies reporting the management of portal vein thrombosis in cirrhosis.*

We have added a new table accordingly.

5. *Although the benefit of endovascular procedures for portal vein thrombosis in cirrhosis is controversial, the authors might add some information in the review article.*

Similarly to what is described for extrahepatic portal vein obstruction in non-cirrhotic patients (Hollingshead M et al, J Vasc Interv Radiol 2005) theoretically, an endovascular approach could be useful to manage PVT also in the context of cirrhosis. However, the experience in the setting of patients with cirrhosis is very limited and hampered by the additional inconvenience that the detection of PVT in this clinical setting is generally incidental and it is difficult to establish the age of the thrombus. The best described endovascular approach is the transjugualr intrahepatic porto-systemic shunt (TIPS). Accordingly, we have introduced the paragraph dedicated to TIPS with the aspects herein reported.

Reviewer 2

The article by Dr. Primignani very nicely summarizes aspects of anticoagulation in patients suffering from liver cirrhosis and portal vein thrombosis, a situation that reflects a clinical dilemma. The manuscript describes important aspects on prophylactic as well as on therapeutic strategies. Furthermore, the author nicely provides arguments that might avoid an inappropriate overrestrictive use of anticoagulants in these patients. However, in my opinion some aspects are missing, which should be discussed more intensively in this manuscript.

Suggestions: #1 The author should describe in more detail the reason, why the conventional coagulation tests do not adequately reflect coagulation in liver patients. The literature suggests that these tests might not predict or correlate with bleeding (Dig Dis Sci 1981;26(5):388-393; Clin Lab Med 2009;29(2):265-282; Hepatology 1986;6(1):79-86) They should provide more aspects on coagulation-testing in liver disease, which could have further implications on decision-making in regard to anticoagulant regimens in these patients. Would an expanded testing of coagulation (e.g. thrombin test and thrombelastography) help in this regard? The author should discuss this point.

Thanks for the comment. We totally agree and have gone more in depth of the problem by also adding the references suggested.

#2 Renal impairment is frequently associated with advanced liver disease. The fact that plasma-levels of certain DOACs can be increased under renal impairment should be discussed in this article.

We agree with this observation and have opportunely included a comment in the text.

#3 The Author should provide a reference for the following assumption. "A platelet count <50x109/L and the use of VKA were the only factors more frequently observed in patients with a bleeding episode suspected to be related to anticoagulation therapy." In addition, I enclose a file of the manuscript with some corrected minor formatting errors.

Thanks to the reviewer for the correction of the minor formatting errors. Indeed we used this file to start our revision of the manuscript in accordance with reviewer's comments. The reference has been opportunely added in the new version of the manuscript.