WORLD JOURNAL OF HEPATOLOGY

Dear Dr. Gioia,

First of all, thank you for submitting your manuscript to the World Journal of Hepatology. Secondly, please be sure to follow all the steps below to modify the proposed manuscript.

Step 1: Verify the accuracy of general information for your manuscript

Name of journal: World Journal of Hepatology

Manuscript NO.: 47737

Column: Opinion Review

Title: NON-CIRRHOTIC PORTAL HYPERTENSION AND PORTAL VEIN THROMBOSIS: WHO CAME FIRST, THE CHICKEN OR THE EGG?

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Reviewer code: 03024263

First decision: 2019-06-20

Science editor: Li-Jun Cui

Step 2: Manuscript revision deadline

The review of your manuscript, which you submitted to the World Journal of Hepatology, is now completed and the first decision for publication is available. We request that you submit your revision in no more than 7 days. If you do not request an extension of this deadline or we do not hear from you about this article within 4 weeks following this first decision, we will assume that you have WITHDRAWN the manuscript from consideration for publication in the World Journal of Hepatology. If you wish to submit the manuscript to another journal within the 4-week time frame, you must first officially withdraw your manuscript from consideration by the World Journal of Hepatology.

Dear Editor,

We would like to thank you for giving us the opportunity to revise the manuscript. All comments were insightful and pertinent, and we appreciated your attention and time.

We have revised the manuscript, and we believe that the revision further improved the results and presentation of our work.

All the tips proposed by the editors have been made and underlined in the revised manuscript.

A point by point replay is following.

Reply to the Reviewers' Comments
Reviewer: 1

"No abstract. In this publication, the authors raise the question of what comes first: idiopathic noncirrotic portal hypertension (INCPH) or portal vein thrombosis (PVT), and discuss the possibility of INCPH in patients with PVT. There are currently a sufficient number of publications showing that INCPH frequently associated with PVT. It may be due to reduced blood flow velocity secondary to the increase in intrahepatic resistance, together with portal vein wall abnormalities. PVT is frequently associated with an underlying pro-thrombotic disorder, worsens INCPH, negatively influencing life expectancy when the diagnosis and treatment is not done at an early stage. As a rule, the prophylactic use of anticoagulants is not recommended. However, in those patients that develop PVT anticoagulant therapy should be started (Baveno VI Consensus). It is possible that patients with non-cirrhotic PVT have morphological changes in the liver by the type INCPH. I do not know. So far this is only a hypothesis. I would like the authors to provide information proving this."

We thank the reviewer for the comments.

Ours is actually a hypothesis and our aim was just to raise the clinical doubt that at least some patients with PVT may be actually affected by a pre-existent and undiagnosed INCPH. In fact, the cause of portal vein thrombosis remains unknown in up to 25% of PVT, despite the active search of local and systemic pro-thrombotic conditions. In our opinion the presence of INCPH should be suspected at least in the group of patients with PVT “sine causa” and the active search of this condition should be included in their diagnostic work-out.

The suspicion of INCPH is high in patients with acute PVT and frank signs of portal hypertension at first presentation after the exclusion of cirrhosis. In the patients with acute PVT without sings of portal hypertension at presentation or in those with chronic PVT, in whom portal hypertension is considered the consequence of PVT, the diagnosis of pre-existing INCPH is very hard. Biopsy cannot be fully discriminant as similar histological data have been described in both conditions. The measurement of HVPG is probably able to distinguish between the two conditions but HVPG measurement is not included in the diagnostic work-out of patients with PVT as PVT is, by definition, a pre-hepatic cause of portal hypertension. Liver stiffness may help, as it has been shown to be higher in the patients with INCPH than in those with “pure” PVT, due to the presence of sclerosis in the portal venous radicles observable in INCPH patients. However, the comparison on liver stiffness between PVT and INCPH is until now restricted to very limited series of patient (see references 10). Thus, we do not have evidence to support our hypothesis until specific studies will be carried on. Our working hypothesis is to perform to liver stiffness all patients with PVT and to summit to a complete diagnostic work-out for the search of INCPH, including the clinical and pharmacological conditions

known to be associated to INCPH. Eventually, the liver biopsy, could be proposed in the PVT patients with a high liver stiffness. However, due to the limited observations described above, the cut off able to select the patients with suspected INCPH among the patients with PVT is still unknown. In conclusion our point of view is still totally hypothetical, but it may have clinical consequence, especially in the decision of suspending the anticoagulation in the patients with PVT and no detectable prothrombotic factors.

A summary of these considerations has been included in the abstract requested.

A new title, alternative to the original, is proposed to avoid the impression that all PVT may be caused by INCPH.

Finally, in the abstract and in the text the term INCPH has been replaced by the new term PSVD (porto sinusoidal vascular liver disease) more recently defined to indicate the disease. *[Cit Andrea De Gottardi, Pierre-Emmanuel Rautou, Jeoffrey Schouten, Laura Rubbia-Brandt, Frank Leebeek, Jonel Trebicka, Sarwa Darwish Murad, Valérie Vilgrain, Virginia Hernandez-Gea, Filipe Nery, Aurélie Plessier, Annalisa Berzigotti, Paulette Bioulac-Sage, Massimo Primignani, David Semela, Laure Elkrief, Pierre Bedossa, Dominique Valla*, Juan Carlos Garcia-Pagan*, on behalf of the VALDIG group. Porto-sinusoidal vascular disease: proposal and description of a novel entity Lancet Gastroenterol Hepatol 2019; 4: 399–411]*