March 18th, 2014

To Lian-Sheng Ma,
President and Company Editor-in-Chief
World Journal of Gastroenterology

**RE: "Major Liver resection and Metabolic Disorders: a postoperative mortality related to an undescribed mechanism."**

**ESPS Manuscript N°**: 8940

**Authors:** Alban ZARZAVADJIAN LE BIAN; Renato COSTI; Mohamed Said SBAI IDRISSI; Claude SMADJA.

Dear Editor-in-Chief,

First, the authors would like to thank you and the referees for your interest in our work and your comments, which have been very useful in order to increase the quality of this manuscript. We respectfully submit a revised version of the paper, which has been modified in accordance with reviewer's criticisms, hoping that it will now be suitable for publication in World Journal of Gastroenterology. As requested, main changes have been highlighted.

My best regards,

Yours sincerely,

Alban Zarzavadjian Le Bian

**Response to the Reviewer**

**Reviewer 1:**

**In this article, Alban "ZARZAVADJIAN LE BIAN" et al present patients who presented with Metabolic Syndrome and died in perioperative course of liver resection. This paper shows the asymptomatic portal hypertension in patients presenting with Metabolic Syndrome (and NAFLD) leads to congestive liver and death after major liver liver resection. This demonstration is of major interest in daily hepatology and in order to understand NAFLD. This is an interesting report for the clinical practice. Overall the report appears to be carefully examined and data adequately discussed. I have a few comments to make.**

**It might be better to add the Metabolic disorders data in Table 2.**

As requested, the Metabolic disorders are now included in table 2 and also re-edited table 1 in order to avoid redundancy.

**How about the relationship between the portal hypertension and the number of Metabolic disorders?**

We agree with the reviewer that the relationship between portal hypertension and metabolic disorders is an interesting point. Unfortunately, the study was retrospectively performed, and the catheterism of the Vena Porta was not systematically performed prior surgical procedure in order to define portal pressure. So, we could not assess portal hypertension in regards of the number of Metabolic disorders. In previous publications, portal hypertension was demonstrated [1,2] and related to liver steatosis (including NAFLD and Metabolic Syndrome). In the manuscript, the presence of portal hypertension was deduced by the development of the hepato-renal syndrome, which notoriously cannot occur without portal hypertension [3].

This limit of the paper is now discussed in the Discussion section.

**Which is the most important factor among Metabolic disorders to affect the portal hypertension?**

As discussed above, we could not assess which metabolic disorder was more important in determining the portal hypertension as we did not routinely measure preoperative portal pressure. Actually, present scientific literature does not show any metabolic disorder as an independent factor in promoting portal hypertension. So, it seems that it is rather the association of multiple metabolic disorders (at least 2, according to our observation) to possibly lead to portal hypertension. Obviously, measuring postoperatively the portal pressure should not have made any sense too, since portal hypertension may also be caused by the surgical resection itself [4] and this would have been a major bias.

This paragraph has been included in the revised manuscript.

**It might be better to change the word. (Such an hypothesis >>> Such a hypothesis) (page 15, line 23)**

The authors performed a minor language polishing in order to correct. In order to simplify revision, language polishing has not been highlighted in the revised manuscript.

**How about the characteristics of other alive patients undergoing liver resection? How about the Metabolic disorders data among these alive patients undergoing liver resection? Didn't they have portal hypertension?**

**It might be better to compare the groups between deceased and alive patients undergoing liver resection.**

Actually, such a comparison was performed and reported in another contribution where selected patients with metabolic disorders undergoing right (or extended right)

hepatectomy were analyzed [5]: in particular, considering the relationship between metabolic disorders and mortality, mortality reached 30% in patients presenting with metabolic syndrome (without other liver disorder) vs 3% in patients with 1 or no metabolic disorders. Moreover we showed that mortality rate rose together with the number of metabolic disorders [5]. Because these results were already published, the authors decided to avoid reporting them again.
In the present manuscript, which includes all dead patients undergoing major liver surgery in our series, we tried to show that the same, specific mechanism is seemingly responsible for such high mortality rate in patients with multiple metabolic disorders, and to suggest a possible better management.
As reported before, it was not possible to measure the portal hypertension since no catheterism was performed prior surgery.
Hopefully, in the future, portal pressure will be evaluated preoperatively to better quantify the surgical risk; prospective, large-sized studies on the subject will evaluate this parameter and its relationship with metabolic disorders. Such considerations are added at the end of discussion.

**Reviewer 2:**

**Zarzavadjian Le Bian et al. made an retrospective analysis of pathogenic mechanisms in perioperative mortality of patients with metabolic syndrome undergoing major liver resection. The topic of the manuscript is important. My main concerns are the small sample size and the lack of novelty of the research.**

We share the reviewer's opinion about the importance and timeliness of this topic. However, we consider that this research does not lack any novelty, as it is the first report of an undescribed sequence of events leading to death and suggesting the pivotal role of portal hypertension in patients with metabolic syndrome (without other liver disorder, including cirrhosis or major fibrosis). The fact that a more appropriate management to interrupt such a sequence is proposed also increases the interest in the paper.

**Specific comments:**

**Ethical approval is missing.**

It was an omission: the Ethical approval is now reported.

**The doses of drugs should be told.**

All patients were treated with Noradrenalin. Max doses prior deciding to discontinue the treatment is now reported in the manuscript.

**The authors should specify all the assay methods (méthode de dosage), give the origin of reagents (origine des réactifs), and explain all abbreviations.**

Abbreviations were explained in the title page. They have been moved to the text of manuscript. Considering Assay methods and origin of reagents, they have been included in the manuscript.

**The authors might discuss the role of inflammation and oxidative stress in the evolution of portal hypertension and hepato-renal syndrome.**

We agree with the reviewer that this is a very interesting topic. An entire paragraph discussing present literature on the subject and possible etiopathogenetic mechanisms based on a very recent experimental study [6] has been added in the discussion section.

Thank you for your interest in our work, and, please, do not hesitate to contact us for any reason.

Yours sincerely,

Alban Zarzavadjian Le Bian, M.D., M.Ph.;

Renato Costi, M.D., Ph.D;

Mohamed Saïd SBAI IDRISS, M.D.;

Claude Smadja, M.D., Ph.D

**References :**


1 Francque S, Verrijken A, Mertens I, Hubens G, Van Marck E, Pelckmans P, Van Gaal L, Michielsen P. Noncirrhotic human nonalcoholic fatty liver disease induces portal hypertension in relation to the histological degree of steatosis. Eur J Gastroenterol Hepatol. 2010; 22:1449-57.

2 Francque S, Laleman W, Verbeke L, Van Steenkiste C, Casteleyn C, Kwanten W, Van Dyck C, D'Hondt M, Ramon A, Vermeulen W, De Winter B, Van Marck E, Van Marck V, Pelckmans P, Michielsen P. Increased intrahepatic resistance in severe steatosis: endothelial dysfunction, vasoconstrictor overproduction and altered microvascular architecture. Lab Invest. 2012; 92:1428-39.

3 Testino G, Ferro C. Hepatorenal syndrome: a review. Hepatogastroenterology. 2010; 57:1279-84.

4 Ueno S, Kobayashi Y, Kurita K, Tanabe G, Aikou T. Effect of prior portosystemic shunt on early hepatic hemodynamics and sinusoids following 84% hepatectomy in dogs. Res Exp Med (Berl). 1995; 195:1-8.

5 Zarzavadjian Le Bian A, Costi R, Constantinides V, Smadja C. Metabolic Disorders, Non-Alcoholic Fatty Liver Disease and Major Liver Resection: An Underestimated Perioperative Risk. J Gastrointest Surg. 2012; 16:2247-55.

6 Aller MA, de las Heras N, Nava MP, Regadera J, Arias J, Lahera V. Splanchnic-aortic inflammatory axis in experimental portal hypertension. World J Gastroenterol. 2013;19:7992-9.