

March 4th, 2017

To Ya-Juan Ma,
Science Editor, Editorial Office
World Journal of Gastroenterology

RE: Consequences of metabolic syndrome on postoperative outcomes after pancreaticoduodenectomy.

Manuscript N°: 32562

Authors: Alban “ZARZAVADJIAN LE BIAN”, David “FUKS”, Sophie “CHOPINET”, Sébastien “GAUJOUX”, Manuela “CESARETTI”, Renato “COSTI”, Ajay P “BELGAUMKAR”, Claude “SMADJA”, Brice “GAYET”.

Dear Sirs,

First, the authors would like to thank you and the referees for your interest in our work and your comments regarding the manuscript. We respectfully submit a revised version of the paper, which has been modified and implemented in accordance with reviewer’s criticisms, hoping that it will now be suitable for publication in International Journal of Surgery.

My best regards,

Yours sincerely,

Alban Zarzavadjian Le Bian

Response to the Reviewer

Reviewer:

I read with interest this paper. It is based on important considerations and the findings are interesting. There are some points to be addressed before considering it for publication, however.

1. The pancreatic parenchyma consistency, soft or hard, was evaluated intra-operatively by the surgeon by manual palpation of the pancreatic remnant. This is not a standardized method. Please write a comment in the discussion section to acknowledge this limitation and to suggest possible solutions for the future. Indeed, the method you mentioned is too subjective to be considered scientifically correct.

The authors do agree with the reviewer's comment: manual palpation is subjective and does not fulfill scientific requirement except for experts, as it is reported as being an appropriate assessment for mild or massive pancreatic steatosis by simple inspection in surgical setting [1]. Because comments 1 and 3 are obviously linked, we implemented a paragraph commenting such a limitation in accordance with reviewer's advice.

2. Have the Authors considered the level of uric acid in these patients? Sometimes this parameter may be altered on such patients and may influence the findings about metabolic syndrome. Please see and cite this paper by Zurlo et al.: High serum uric acid levels increase the risk of metabolic syndrome in elderly women: The PRO.V.A study. Nutr Metab Cardiovasc Dis. 2016 Jan;26(1):27-35.

The authors did not consider level of serum uric acid as it is not routinely performed and is not anymore seen as a criterion enabling to reach Metabolic Syndrome

diagnosis. However, in accordance with the reviewer's comment, we implemented in the manuscript the reference and the reason serum uric acid was not used for the purpose of this study in the methodology.

3. Which is the role of pathologists in evaluating the pancreas? Fatty versus non fatty pancreas is a parameter that should be evaluated by the pathologists. Indeed, a hard pancreatic parenchyma is present not only in case of a florid acinar architecture, but also in case of desmoplastic reaction (fibrosis due to cancer) or in case of fibrosis for inflammation (pancreatitis,...). Please state clearly if there is a role for pathologists, in this case is this role standardized?, and please clear state that a possible strategy to ameliorate the research in this field will be in the future the involvement of pathologists in these studies.

First, the authors would like to thank the reviewer for these queries regarding histopathology.

In regards of pancreaticoduodenectomy, there is currently no major change in surgical management related to fatty pancreas in spite of the link between fatty pancreas and pancreatic fistula. Indeed, no mean has been demonstrated as decreasing specifically this complication in this background, resulting in lack of interest for preoperative or intraoperative assessment.

Consequently, we may wonder the role of pathologist in fatty pancreas as it is not standardized. In current clinical practice, fatty pancreas is defined using pathological examination [2]. Yet, it can be uneven in pancreas [3], compelling to propose another method to assess fatty pancreas in preoperative or intraoperative settings. MRI is currently considered as being as effective as histology when assessing fatty infiltration [4]. Still, a consensual and standardized histopathological examination assessing fatty infiltration [2] and fibrosis [5] of pancreatic parenchyma is required, as it has been proposed in Non-Alcoholic Fatty Liver Disease (NAFLD) [6]. Also, like in NAFLD, microcirculation disorders should be investigated in fatty pancreas: in NAFLD, microcirculation has been reported as being altered [7] potentially leading to an increased mortality after hepatectomy [8]. Ischemic process related to

microcirculation disorders in fatty pancreas could explain an increased rate of pancreatic fistula.

In accordance with the reviewer comments, these answers have been implemented in the manuscript in order to improve its quality.

Finally, language editing was performed.

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, MD, PhD

David Fuks, MD, PhD

Sophie Chopinet, MD

Sébastien Gaujoux, MD, PhD

Manuela Cesaretti, MD,

Renato Costi, MD, PhD

Ajay Belgaumkar, MD

Claude Smadja, MD, PhD

Brice Gayet, MD, PhD

- 1 Verma AR, Papalois V. Evaluating steatosis in pancreatic transplant. *Exp Clin Transplant*. 2011;9:159–164.
- 2 Smits MM, van Geenen EJ. The clinical significance of pancreatic steatosis. *Nat Rev Gastroenterol Hepatol*. 2011;8:169–177.
- 3 Matsumoto S, Mori H, Miyake H, Takaki H, Maeda T, Yamada Y, Oga M. Uneven fatty replacement of the pancreas: evaluation with CT. *Radiology*. 1995;194:453–458.

- 4 Lingvay I, Esser V, Legendre JL, Price AL, Wertz KM, Adams-Huet B, Zhang S, Unger RH, Szczepaniak LS. Noninvasive quantification of pancreatic fat in humans. *J Clin Endocrinol Metab.* 2009;94:4070–4076.
- 5 Klöppel G, Maillet B. Pseudocysts in chronic pancreatitis: a morphological analysis of 57 resection specimens and 9 autopsy pancreata. *Pancreas* 1991;6:266–74.
- 6 Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, Ferrell LD, Liu YC, Torbenson MS, Unalp- Arida A, Yeh M, McCullough AJ, Sanyal AJ. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005; 41:1313-1321.
- 7 McCuskey RS, Ito Y, Robertson GR, McCuskey MK, Perry M, Farrell GC. Hepatic microvascular dysfunction during evolution of dietary steatohepatitis in mice. *Hepatology.* 2004; 40:386-93.
- 8 Zarzavadjian Le Bian A, Costi R, Sbai-Idrissi MS, Smadja C. Liver resection and metabolic disorders: an undescribed mechanism leading to postoperative mortality. *World J Gastroenterol.* 2014; 20:14455-62.