

December 30th, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7728R1.doc).

Title: Metabolic syndrome and NAFLD in liver surgery: The new scourges?

Author: François Cauchy, David Fuks, Alban Zarzavadjian Le Bian, Jacques Belghiti, Renato Costi

Name of Journal: World Journal of Hepatology

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The manuscript has been improved according to the suggestions of reviewers:

1. English language has been reviewed by a native English professional translator: Clemence Sebag; e-mail: clemencesebag@gmail.com
2. Format has been updated
3. Revision has been made according to the suggestions of the reviewer

Reviewer 1:

This review by Cauchy and coworkers is based on few data available in the literature and I do not think it is time to publish a review on this topic. We have to wait new well-designed study in order to be able to develop meta-analysis of the data. The only "new" things are the one reported in Table 2. I don't think this paper is suitable for publication on WJG.

We thank the reviewer for this comment. We do agree that the paucity of available data in the literature does not allow achieving a high level of evidence and that new well-designed studies are indeed waited. Nevertheless, in our clinical practice we had to face several issues that are addressed in this review. Therefore, we felt important to inform gastroenterologists and hepatologists that the underestimated risk in patients with MS/NAFLD may lead to avoidable morbidity/mortality.

Reviewer 2:

Regarding the manuscript entitled "Metabolic syndrome and NAFLD in liver surgery: The new scourges?", there are some minor comments:

1. This manuscript comes at a time where several publications exist in the literature on this topic; therefore, the authors need to emphasize the novelty and impact of their articles to be considered for publication.

We thank the reviewer for this important comment. We have modified the manuscript in order to emphasize the novelties, which are discussed in this review.

2. The authors could include in their review also the recent paper by Fierbinteanu et al, Journal of Physiology and Pharmacology, 2013, 64, 1, 3-9, which showed the major health impact of NAFLD.

We agree with the reviewer and have therefore added this reference in the revised version of the manuscript.

Page 4, **“As its incidence parallels that of the MS, NAFLD is currently becoming one of the first chronic liver diseases in Western countries and therefore has a major health impact^[3]”**

Reviewer 3:

Interesting review. Famous team. Expert team of the field.

1. Page 7: Delete the sentence: "Although false positive may be recorded,[32] histological analysis remains the gold standard for the assessment of NAFLD by using the non-alcoholic liver disease activity score (NAS) proposed by Kleiner et al.[25]" The diagnosis must be done by a trained pathologist as written in the next part of the manuscript. Published scores can be useful for the diagnosis (Brunt's classification, Bedossa's classification-Please add the reference: Hepatology. 2012 Nov;56(5):1751-9. doi: 10.1002/hep.25889. Histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients. Bedossa P, Poitou C, Veyrie N, Bouillot JL, Basdevant A, Paradis V, Tordjman J, Clement K.) or to follow patients but not for the diagnosis (NAS). This must be added in the paper.

In line with this comment, we have removed the above mentioned sentence and have modified the paragraph regarding the limits and utility of histological assessment.

Page 7, **“ ... and should be performed by a trained pathologist^[33]. Several histological scores might be useful for diagnosis. The most frequently used score is the non-alcoholic liver disease activity score (NAS) proposed by Kleiner et al^[26], Likewise, Bedossa et al. recently published a histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients^[34]”**

2. Table 1: Change "Other inappropriately used criteria" this is true only for parameters associated with the central obesity. For the other parameters, precise that treatments must be taken in account except if given in preemptive purpose(s).

In line with this comment, we have changed the expression “Other inappropriately used criteria” to “other non-consensual criteria” and have added a sentence stating that **“these treatments can be taken in account for the diagnosis of MS unless if given in preemptive purpose”**

Reviewer 4:

The entire manuscript must be revised to fix English grammar errors and the punctuation; although the topic is interesting, the reading results difficult for these two reasons.

We thank the reviewer for his willingness to improve the clarity of our manuscript. In line with his comments the manuscript has benefited careful restyling and has been reviewed by a native English professional translator.

1. The abstract need a careful restyling:
 - a. For instance, the first sentence “The aim of this topic highlight is to analyze the emerging evidence...” is neither correct nor fluent.
 - b. Please clarify the abbreviation “HPB” in the abstract.
 - c. Some statements, such as “NASH related cirrhosis is a rising etiology of end stage liver disease, potentially leading to transplantation” are far from being evidence based and even meaningful.

In line with the reviewer’s comment we have deeply modified the abstract and have clarified the abbreviation “HPB”.

2. The Core tip “There is an emerging evidence that the metabolic syndrome (MS) and its liver manifestation, the non-alcoholic fatty liver disease (NAFLD), are associated with the development of primary liver neoplasias and poor results of major liver surgery” is a collection of not well-supported statements.

The core tip has been almost entirely changed in the revised version of the manuscript.

Page 3, **“Core tip: The metabolic syndrome (MS) and its hepatic manifestations, the non-alcoholic fatty liver disease (NAFLD), are increasingly observed in western countries. Both MS and NAFLD could favor the development of primary liver malignancies and may also lead to end-stage liver disease. These patients are at higher operative risk because of underestimated postoperative liver related complications but also specific increase in cardio-vascular complications. Specific improvements in the perioperative management of these patients are required in order to improve the operative results”**

3. The introduction is repetitive, please make it more fluent and realistic and less catastrophic: “NAFLD liver histopathological alterations range from simple steatosis to steatohepatitis, to fibrosis and may end up in true cirrhosis leading to end stage liver disease, potentially needing transplantation”.

In line with this comment, the introduction has been changed in order to be more realistic and less catastrophic.

4. The aims of the review: "1 The objectives of this review are therefore to provide comprehensive insights regarding the current standards and issues in the diagnosis of both MS and NAFLD, 2 to clarify their respective impact on tumor progression as well as 3 their influence on postoperative outcome. Finally, 4 the issue of the measures that should be undertaken in upcoming years in order to improve the results of surgery are addressed. Please, check how these four aims of this review are developed.

We thank the reviewer for this comment allowing us to provide a more structured paper. We have modified the sentence in order to stick to the developed aims.

Page 5, "... (i) to provide comprehensive insights regarding the current standards and issues in the diagnosis of both MS and NAFLD; (ii) to clarify their respective impact on tumor progression as well as their influence on postoperative outcome; (iii) to discuss the measures, which should be undertaken in upcoming years in order to improve the results of surgery."

5. The sentence "In fact, histological alterations (NAFLD) may also rise in patients presenting with individual components of the MS including diabetes mellitus (DM), hypertriglyceridemia and obesity" must be reformulated. The topic of the paragraph is the metabolic syndrome and, after a brief introduction and definition, this sentence must be better linked to the previous one.

This sentence has been reformulated in accordance to the reviewer's comment.

Page 5, "**Even-though, the presence of at least 3 out of 5 criteria of the consensual definition are required to define the MS^[1] both liver histological manifestations and influence on surgical outcomes after liver surgery may occur in patients presenting with individual components of the MS. Indeed, fatty liver disease may also occur in patients with isolated diabetes mellitus (DM)^[14], hypertriglyceridemia^[15] and obesity^[16,17]...**"

6. "Histological alteration" is too generic and the word "NAFLD" in parentheses doesn't clarify the concept. I suggest to change it for example with "Histological liver alteration" or simply "Fatty liver disease".

In line with the reviewer's comment, the expression "Histological alteration" has been changed for "fatty liver disease".

7. Section Metabolic syndrome In the sentence "Interestingly, most of the studies including retrospective medical and surgical literature do not always gather all these consensual criteria but rather use substitutes for commodity", I think that the word commodity is used instead of the colloquial Italian "comodità", but the real meaning is another one. So I suggest to modify and substitute it with "for convenience".

We apologize for this mistake and thank the reviewer for pointing it out. As a matter of fact, the word commodity was used instead of the French word “commodité” which indeed arises from the latin word “commoditatem or commodus”. The meaning is indeed another one and we have therefore substituted this word with “for convenience”.

8. Section non-alcoholic fatty liver disease (NAFLD). In the sentence “NAFLD has emerged as one of the most frequent forms of chronic liver disease in Western countries and should be considered in case of steatotic infiltration exceeding 5% of liver parenchyma at histology in the absence of previous or ongoing significant alcohol consumption”; I suggest to substitute “steatotic infiltration” with “fatty infiltration”.

The expression “steatotic infiltration” has been changed for “fatty infiltration” in accordance to the reviewer’s suggestion.

9. Section non-alcoholic steatohepatitis (NASH). In the sentence “Moreover, NAS does not include other histologic alterations often present in NAFLD, such as microcirculation modifications, which are not routinely reported by pathologists and whose role in progression from MS to NAFLD still have to be defined..” the word “ not” is often repeated, please fix it.

Here again we thank the reviewer for pointing out this typing mistake which was corrected in the revised version of the manuscript.

10. “Interestingly, Brunt et al. have emphasized that the diagnosis of NASH based on evaluation of patterns as well as individual lesions on liver biopsies did not always correlated with threshold values of the semi quantitative NAS. Moreover, NAS does not include other histologic alterations often present in NAFLD, such as microcirculation modifications, which are not not routinely reported by pathologists and whose role in progression from MS to NAFLD still have to be...???”

We deeply apologize but the rest of the comment was not available. Nevertheless, the rest of the manuscript was restyled and we hope that it will now be suitable for publication.

4. References and typesetting were corrected

Thank you again for publishing our manuscript in the World Journal of Hepatology.

Sincerely yours,

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