

Barcelona, May 31, 2018

Dear Mr. Lian-Sheng Ma, Founder and Chief Executive Officer of World Journal of Gastroenterology, and reviewers,

We would like to thank you for your constructive comments that helped to improve our manuscript entitled: "**Expansion of the Hepatocellular Carcinoma Milan criteria in Liver Transplantation - where are we heading?**" by Pavel MC and Fuster J (Number ID: 00069810). As you will see bellow, we addressed the concerns that were raised and we have modified the manuscript accordingly. In order to assist Reviewers, **comments from editors and reviewers** are reported in bold, replies in regular type whereas *sentences added or corrected in the revised manuscript* are in italic in the point-by-point response

We greatly appreciate the opportunity to submit this revised manuscript and hope it is now suitable for publication in World Journal of Gastroenterology,

Sincerely,

Mihai-Calin Pavel, MD, PhD

Comments from the reviewers

Reviewer 1

The authors review the current status of LT beyond Milan criteria in three different scenarios that are all important in clinical practice. They comprehensively referred appropriate publications most of that are milestones in the topics. Therefore, this review will be beneficial for the WJG readers. There are a few questions and issued to be addressed. 1. In “The effect of expanding beyond Milan criteria on the liver transplantation waiting list” section, the authors discussed over the effect of expanding beyond Milan on the effect on the post-transplant survival of all the patients in the waiting list. How about the overall survival of all the patients in the waiting list including those who had been lost without LT, since as the authors pointed out, those increasing number of patients will be lost before LT because of the increased number of candidates in the waiting list. 2. Even if the expanding beyond Milan increased the candidate in the waiting list, the reviewer believe it may not be harmful, if an appropriate criteria for the order of waiting list have been applied. 3. In the “Future directions”, Line 4. There is a redundant “that”.

First of all, we would like to thank to the reviewer for his comments. Regarding the questions, we would like to comment the following:

1. Related to the effect of the expansion on all the patients in the waiting list, we believe that this matter was addressed when describing the article of Volk ML et al (Am J Transplantation 2008, ref 21 in our article). The aim of this study, as described in our article, was to examine what effect would have the expansion of HCC criteria for LT on the waiting list across the pre- and postLT periods. The 61% 5-year survival is actually a threshold needed in order to outweigh the harm for the other patients in the waiting list.
2. We agree with the reviewer that with a good selection of the LT candidates, the expansion should be associated with favorable results. However, we also believe that more evidence is needed in order to firmly demonstrate this fact.
3. *We corrected the redundant “that”*

Reviewer 2:

Major Comments: This manuscript provides an overview on experiences with the expansion of the Milan criteria in liver transplantation for hepatocellular carcinoma. Some items remain vague and further studies are needed, but this

is, of course, not the fault of the authors. The contributions of each of the authors should be specified. **Minor Comments: Language polishing is required; e.g. "Two conclusion can be drawn from this study", "In the last reports of the US transplant registry, the HCV is no longer the principal indication for liver transplantation, being overcome by the HCC and the alcohol", etc. Some sentences are incomplete ("The main advantage of the Metroticket is that, by offering individualized survival predictions, could play a role in the regional organ allocation process") (??) or contain too many words ("By diminishing the HCV indication for LT, the liver grafts that that no longer would be necessary for these patients could be used to explore the expansion beyond MC"). Please correct the typing errors (e.g., "cavaveric", "togheter", "OS - overall surviva") as well**

We would like to thank to the reviewer for his comments. Both authors contributed equally to the article. We performed the requested corrections.

Changes performed:

- *"Two conclusion can be drawn from this study" changed to "Two conclusions can be drawn from this study" (page 6, last line of the manuscript)*
- *"In the last reports of the US transplant registry, the HCV is no longer the principal indication for liver transplantation, being overcome by the HCC and the alcohol" changed to "In the last reports of the US transplant registry, the HCV is no longer the principal indication for liver transplantation, being overcome by the HCC and the alcohol" (page 10, line 16 of the manuscript)*
- *"The main advantage of the Metroticket is that, by offering individualized survival predictions, could play a role in the regional organ allocation process" changed to "By offering individualized survival predictions, the Metroticket could play a role in the regional organ allocation process" (page 12, line 4 of the manuscript)*
- *"By diminishing the HCV indication for LT, the liver grafts that that no longer would be necessary for these patients could be used to explore the expansion beyond MC" changed to "The liver grafts that are no longer needed for the HCV patients could be used to explore the expansion beyond MC" (page 15, line 3 of the manuscript)*
- *Typing errors corrected: "cavaveric" to "cadaveric" (page 15, line 8 of the manuscript), "togheter" to "together" (page 13, line 16 of the manuscript), "OS*

- overall surviva" to "OS - overall survival" (page 17, Abbreviations) and "Abrreviations" to Abbreviations (page 17 Abbreviations)

Reviewer 3:

This is a fine review on some specific and important topics in the context of liver transplantation in Milan Out HCC patients. The topic is of current importance, the manuscript is well written and easy to follow. Apart from that, to my opinion, the authors have drawn the right conclusions from the stated literature. What makes this review different from other Reviews in this field is the concentration on three major issues that we are currently dealing with.

We would like to thank to the reviewer for the very nice comments.

Reviewer 4:

This review deeply analyzed the Expansion of the Milan criteria of Hepatocellular Carcinoma for Liver Transplantation. A good review for the topic.

We would like to thank to the reviewer for the very nice comments.