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7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

Dear editor in chief of World Journal of Clinical Cases

We have received the comments of the editor in chief and the reviewers. We are grateful to all of them because all the critiques will strengthen the quality of our study. We have tried to make the necessary changes. In various parts that could not be changes, we have given the proper responses to the reviewers. Selection criteria according to morphometric characteristics have short comings. Furthermore, there are still patients with tumors beyond any defined criteria but have favorable outcomes following liver transplantation. Therefore, answer lies in determining tumor biology which is very heterogenous and also development of therapeutic agents effective in neoadjuvant and adjuvant setting is necessary, therefore evolution of the current criteria must be known as well as the basic knowledge of targeted therapies is required to guide future research. In the present study we tried to give this perspective and we summarized all of these topics in various parts of our article

We hope that you will consider publication of our study in World Journal of Clinical Cases**.** We hope to hear from you soon,

Sincerely Yours

Correspondence to:

Sami Akbulut, MD, PhD, Prof, FACS

Department of Surgery

Department of Public Health

Department Biostatistics and Medical Informatics

Inonu University Faculty of Medicine,

Elazig Yolu 10. Km

Malatya 44280, Turkey.

Telephone: +90-422-3410660

Fax: +90-422-3410036

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7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

Email: akbulutsami@gmail.com

Responses To The Comments

Name of Journal	World Journal of Clinical Cases
Manuscript NO	77520
Title	Liver Transplantation For Hepatocellular Carcinoma: Historical Evolution of Transplantation Criteria
Author List	Volkan Ince, Tevfik Tolga Sahin, Sami Akbulut and Sezai Yilmaz

COMMENT FROM EDITOR IN CHIEF

I recommend the manuscript to be published in the World Journal of Clinical Cases. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

RESPONSE

We have applied the tool and we have obtained only three articles. We are including our output document regarding our research in RCA database. One of the two of the studies are from our team and one of them is a congress abstract which is not informative. We have read and added the remaining two studies to the first

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paragraph of the "Future Perspectives" section. On the other hand, our main goal is to convey tour opinion regrading treatment of HCC including LT. In our opinion, there will never be an ideal selection criteria and in future the results of the basic science research will provide two main tools: i)ideal markers sets to determine the biologic behavior of the tumors and ii) better systemic therapeutic agents for neoadjuvant and adjuvant therapeutic settings. These can be seen from the evolution of the patient selection criteria. Today will guide the future, as there is no ideal criteria today the same will happen in future because we are dealing with a heterogenous tumor subset.We believe this article should be evaluated in this context.

Reviewer ID: 05914859

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

SPECIFIC COMMENTS TO AUTHORS

The paper present an exhaustive review of the scoring systems for liver transplantation, therefore maybe you should stick just on this and propose another paper that deals the bridging procedures and the future directions.

RESPONSE

We would like to thank the reviewer for the positive criticism. In previous critiques from the BPG group, a section regarding the bridging procedure was advised to be added. It is our opinion that liver transplantation for hepatocellular carcinoma should be evaluated under two concept; living donor liver transplantation and deceased donor liver transplantation. Living donor liver transplantation of the patients with hepatocellular carcinoma that is beyond Milan criteria should be discussed with in the context of response to downstaging procedures. On the other

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hand, in countries where deceased donor liver transplantation is abundantly performed, patients on the waiting list should undergo bridging procedures to prevent drop-out. For these reasons, locoregional therapies are integral part of transplant selection criteria for hepatocellular carcinoma. Another point that should be emphasized is the biologic response of the tumors to these procedures as a mode of neoadjuvant therapy determines the post-transplant survival. Therefore, we summarized these studies in this subsection. In either way, we have revised and shortened this section and only the key points are given.

Reviewer ID: 02936034

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

SPECIFIC COMMENTS TO AUTHORS

Liver translation is an important treatment for the patients with HCC.However,which patients should receive liver translation is still controversial. This manuscript summarizes the development of criteria of liver translation for hepatocellular carcinoma(HCC) and down-staging procedures for patients beyond Milan criteria or other criteria. In general,it is a good review,but the topic of this manuscript is not novel. Too many articles are published to discuss this topic. The authors introduce their own criteria--Malatya and expanded Malatya criteria,which is the fancy part of this paper.In general, it is a good and comprehensive paper. 1.The history of selection criteria can be tighter, and the introduction of Malatya criteria can be more detailed. 2.In your manuscript, there still exist some mistakes need check and correct . In Page 4 line 14,"Therefore, using a valuable resource for patients with malignancy should beIn general,LT for any disease is considered acceptable if 5-

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years survival rate is ≥ 50%" In page 12 line 26," the results of LDLT for HCC were comparable to that f DDLT in terms of recurrence rates and disease-free survivals"

RESPONSE

We would like to thank the reviewer for the critiques. We have made the necessary grammatical corrections and checked the document for further grammatic errors. The changes have been marked in red.

In accord with the suggestions of the reviewer, we have made the "Historical Perspective" section shorter. Also we made the sections regarding extended criteria shorter as well. The organization of the section titles "**Extending beyond the Milan Criteria: Expand or not to Expand?**" is as follows: i) development of UCSF criteria which has showed that patients with HCC extending beyond Milan can still be treated with LT with a favorable outcome, ii) Development of markers of tumor biology have been discussed in the context of more recently developed extended criteria, iii)Definition of Malatya and extended Malatya criteria have been explained. We did not give more detail about the Malatya and extended Malatya criteria for the current form gives the key points regarding our criteria for patient selection. As other sections became more concise, the part explaining Malatya criteria became more dominant.

Reviewer ID: 05908713

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Rejection

SPECIFIC COMMENTS TO AUTHORS

I read with great interest this review about the historical evolution of liver transplantation criteria. Despite the big effort, I found it not coherent with its aims. It

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doesn't add any knowledge to the readers, neither is able to summarize the argument. In particular, when dealing with current limitations and future perspectives, the authors talk about the medical therapy of HCC, while not focusing on the main aim of selection criteria: give benefit to the "right" patients, trying to overcome the constant organ shortage. The authors should focus on actual drawbacks of the many existing criteria, and on the possible ways to overcome them. According to ILTS ideal criteria should deal with tumor biology , organ availability in the geographical area, probability of waitlist and post-LT survival (i.e., transplant benefit), and waitlist composition. The paragraph about downstaging is too long and doesn't deal with the selection criteria, it should be treated just with few sentences within the text.

RESPONSE

We would like to thank the reviewer. We have made the section on the locoregional therapy more concise and formed it on to a single paragraph giving the pearls of the subject. We have specially added this section in accord with the previous critiques of the BPG group. Furthermore, we believe that the biologic behavior of the tumor to the locoregional therapies is and will be the mainstay of the selection criteria for the patients with HCC for liver transplantation. This is especially true for the era of the living donor liver transplantation. Therefore, we believe that this section should be left in place because in future it will be even more important to evaluate the response to locoregional therapies to determine the outcome of the patients following liver transplantation.

As for the future directions, previous reviewers of the BPG group have advised us to review the current therapeutic options for HCC in this section. The main problem with the current selection criteria and the scoring systems is the consequences of level of exceeding the Milan criteria which is the increase in the locoregional and distant recurrences following liver transplantation. Especially in countries such as

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ours (Turkey), living donor liver transplantation offers possibilities of transplanting patients with HCC without compromising the deceased donor organ waiting list. Furthermore, life time of research may not provide the "ideal criterion" for patient selection for LT. In fact, this is the main ideal behind this review; "one size does not and will not fit all". Therefore, there is only one controllable parameter in the setting of HCC treatment, which is developing effective systemic and locoregional therapeutic alternatives. Similarly, diagnostic packages to determine various poor prognostic factors of the treated tumors should be developed to assist personalized therapeutic approaches.

The first strategy to extend patient survival in HCC tumors exceeding Milan Criteria is providing effective systemic therapy. Therefore, although we respect your ideas, we do not agree with your criticism regarding our manuscript being out of context. The future of these patients lies in developing better systemic therapies that will assist in neoadjuvant and adjuvant setting. Second strategy is to develop demonic and/ or biologic marker sets to thoroughly evaluate the tumor biology of the patient which is in our opinion the future of the selection criteria. In this case the patients with poor genomic or biologic markers will be excluded from transplantation even if their tumor is within the current acceptable criteria.

In order to clarify our aim, we have added a paragraph in the beginning of the "Future Directions section" to support our opinion for the subject.