November 7, 2018

Dear World Journal of Hepatology Editors and Reviewers,

Thank you for your recent review of our paper titled *Recent Dramatic Increase in Liver Transplantation for Alcoholic Liver Disease.* We appreciate the time you put into improving the quality of our manuscript and we have addressed the issues raised as follows:

1. **I do not see the concordance between the title, aim and data presented. Most data are regarding the patients characteristics over time, but not of the "indications", which I understand it related to the criteria for transplantation. This part is discussed but it still remains unclear what is the cause of the increase. The title should specify that the data presented is in the US population. [Reviewer 2] The definition of 'dramatic' is subjective. Some people would argue that this increase observed is significant but not high enough to warrant this description. [Reviewer 3]**

We agree that the title is subjective and could be modified to better represent the scope of the paper. We have changed the title to reflect these sentiments, in addition to noting the country in which the study occurred. The new title is *Recent Trends in Liver Transplantation for Alcoholic Liver Disease in the United States.* We have also updated the aims statement in the Introduction.

2. **What is meant by "The increase corresponds, but is incompletely explained by a decrease in transplants for hepatitis C – alcoholic liver disease dual listing." [Reviewer 1, Core Tip]**

Thank you for allowing us to clarify this point. One hypothesis we had about why the number of transplants for ALD is increasing is that treating patients for Hepatitis C, would result in fewer patients listed for transplant with a dual-listing diagnosis of Hepatitis C and ALD (HCV/ALD). Instead, these patients would be listed with a diagnosis of ALD. To examine this, we compared the decrease in listings for HCV/ALD (-90.7 transplants per year comparing the before and after eras) to the increase in listings for alcoholic cirrhosis (+207.5 transplants per year). Thus, we theorize that the cure for HCV and subsequent change in cirrhosis etiology could explain part of the increase we see (90.7/207.5) but does not completely explain the change.

3. **References 3 and 4 need updating. [Reviewer 1]**

We agree, and they have been updated.

4. **For the international audience, a map or explanation of the UNOS regions may be helpful. [Reviewer 2]**

Thank you for assisting us in appealing to a more international audience. We have included a statement in the Methods section about UNOS's role and a map (Figure 3) showing the UNOS regions.

5. **Have there been changes in the guidelines established by the hepatologists for liver transplant in ALD patients? by the AASLD or others? that may explain this increase. [Reviewer 2] "Lastly, a change in transplant center selection criteria allowing more lenient sobriety criteria could also help explain our findings." (Please clarify the cause of this increase in LT for ALD) [Reviewer 1]**

Thank you for this thoughtful question as we try to delve further into reasons explaining the observed increase. The AASLD Practice Guidelines for alcoholic liver disease were last updated in January 2010[1]. The AASLD 'Evaluation for Liver Transplantation in Adults' Practice Guidelines was updated in 2005[2] and again in 2013[3]. Both the 2005 and 2013 guidelines discuss a 3 to 6 month sobriety period, although the wording has changed. In 2005 there was an official recommendation of "it is prudent to delay transplantation for a minimum of 3 to 6 months of abstinence from alcohol," and in 2013 there was no formal recommendation of an abstinence period but instead a focus on early referral for liver transplantation. While there is not a temporal relationship between the publication of this paper (March 2014) and the increase in ALD seen in our paper (start of 2013), the 2013 Guidelines may reflect the sentiment of the time and a developing leniency of the abstinence requirement. This has been reflected by a statement in the Discussion section and adds clarification to the sentence brought to our attention by Reviewer 1.

6. **"We examined only patients transplanted for ALD, not those listed for transplantation, so we are unable to determine whether the increase observed is due to an increasing listing for ALD or an increase in the proportion of waitlisted patients with ALD undergoing transplant" (This is a catastrophic limitation) [Reviewer 1, Discussion]**

Thank you for this critical feedback. A recent paper, cited earlier in the manuscript, contains data on the change in the number of new waitlisted patients with ALD[6]. The authors found that although the number of new waitlisted patients with ALD is rising, it is not rising as fast as the transplants for ALD. This paragraph in the Discussion section was changed to reflect this additional information.

7. **In the discussion, it may be relevant to add if the same trend is reported in other regions of world, so that this data is placed in perspective [Reviewer 2]**

Thank you for your suggestion. We have added comments to the Discussion regarding liver transplant in other regions of the world.

8. **I think the discussion of the screening tools for alcohol use is excessive for this manuscript and can be omitted. [Reviewer 3] The CAGE (give the full name) questionnaire [Reviewer 1]**

Thank you for this feedback. In reviewing the paper we agree that this paragraph is too long but feel that it is important to present a potential intervention for our findings of increasing ALD. Thus, we have shortened the paragraph. Please note that the CAGE questionnaire is not an abbreviation and does not have a full name to include.

9. **Why transplantation for this older age(>65y)? And what is the outcome of patients with this old age after LT? [Reviewer 1, Methods] Why transplantation for this high MELD? And what is the outcome of patients with this high MELD after LT? [Reviewer 1, Results]**

Thank you for your thoughtful question. It is beyond the scope of this paper to delve into the reasons why and the outcomes of liver transplantation for those over 65 years old and for those with high MELD. However, other authors have shown that an increasing proportion of liver transplants done in patients ≥ 60 years old (41% in 2014) and that transplant-related survival benefit in older patients is similar to that of younger patients[4]. A group out of Switzerland performed a propensity-matched analysis of high-MELD (MELD≥30) versus low-MELD (MELD<30) liver transplant recipients, and found that 5-year survival was only 8% lower (70% vs 78%), which was not statistically significantly different[5].

References:

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4. **Su F**, Yu L, Berry K, Liou IW, Landis CS, Rayhill SC, Reyes JD, Ioannou GN. Aging of Liver Transplant Registrants and Recipients: Trends and Impact on Waitlist Outcomes, Post-Transplantation Outcomes, and Transplant-Related Survival Benefit. *Gastroenterology*. 2016;**150**:441-53.e6. [PMID: 26522262 DOI: 10.1053/j.gastro.2015.10.043]
5. **Schlegel A**, Linecker M, Kron P, Gyori G, De Oliveira ML, Mullhaupt B, Clavie PA, Dutkowski P. Risk Assessment in High- and Low-MELD Liver Transplantation. *Am J Transplant*. 2017;**17**:1050-1063. [PMID: 27676319 DOI: doi: 10.1111/ajt.14065]
6. **Goldberg D**, Ditah IC, Saeian K, Lalehzari M, Aronsohn A, Gorospe EC, Charlton M. Changes in the Prevalence of Hepatitis C Virus Infection, Nonalcoholic Steatohepatitis, and Alcoholic Liver Disease Among Patients With Cirrhosis or Liver Failure on the Waitlist for Liver Transplantation. *Gastroenterology* 2017; **152**: 1090-1099.e1. [PMID: 28088461 DOI: 10.1053/j.gastro.2017.01.003]

Thank you for considering our resubmitted manuscript. We look forward to hearing back from you.

Sincerely,

Lena Sibulesky