

Manuscript Review Response Letter

Dear esteemed reviewers,

Thank you for taking the time to review our manuscript. We greatly appreciate each one of your input and hope the changes we have made highlighted below improve our study's message. See below for the revisions made based on comments provided by the reviewers. Our responses and revisions can be found below, pointwise and in detail under excerpts from the reviewers' comments.

Sincerely,

The study authors

Reviewer #1 (00503441):

Comment: The paper is well written and easy to follow. The Reviewer has just some points to address. The principal strength of the study is given by the relevant number of patients enrolled in the study. The principal weakness is the retrospective characteristic of the cohort study. Moreover, the Authors should specify why did not include also patients undergone TIPS for varices other than for refractory ascites.

Answer: Thanks for the encouraging comments and we agree with the limitations of a retrospective study. We did not include patients undergoing TIPS for varices in order to create a more homogeneous study group, specifically those undergoing TIPS for refractory ascites. This is elaborated further in the methods section.

Reviewer #2 (02539873):

Comment: The manuscript is written in a quite chaotic way, so it is not easy to follow the Authors' conception for the presentation of the study. The statements should be more concrete and followed by discussion/explanation of the results obtained, eg. "TIPS was found to increase time on waitlist in patients with ascites." - try to explain why?

Answer: We are thankful for your suggestions and made changes in our paper as per your suggestions and concerns:

1. TIPS was found to increase time on waitlist in patients with ascites- Page 11 will read: "We found that increased time on the waitlist in the TIPS group was consistent with findings from single center studies^[20]. ...The increased time on LT wait list may be explained by decreased portal hypertension produced by the TIPS and mortality that comes with complications of portal hypertension. "

2. See more broad revisions to discussion section, which aimed to separate out each main finding and explain why we thought that result was seen.

Comments: I have found several inaccuracies.

page 6- "Operative mortality and early graft function were found not to be influenced by TIPS placement during (?) liver transplantation"

Answer: These changes are added in the revised manuscript on page 6: "When comparing TIPS vs non-TIPS patients, studies revealed comparable transfusion requirements and operative time between the two cohorts and also demonstrated operative mortality and early graft function not to be influenced by TIPS placement^[9-10]. "

Comment: page 6 "Transjugular intrahepatic portosystemic shunts (TIPS) plays- should be plural

Answer: Thank you for pointing out this mistake. It is corrected as "Transjugular intrahepatic portosystemic shunts (TIPS) play an important role in the treatment of recurrent esophageal varices, bleeding gastric varices and refractory ascites. "

Comment: BMI is not a reliable tool for cirrhotics assessment- it is biased by accumulation of fluid in peritoneal cavity.

Answer: We agree with your comment, however, unfortunately, the UNOS database limited our ability to include alternative tools for estimation of body weight. BMI is used in many UNOS based studies, therefore, we also used it in our report.

Comments: The description of the study cohort selection is not clear; exclusion and inclusion criteria are repeated in different parts of the manuscript, but not described clearly:

page 7- "All patients with TIPS for ascites who ultimately underwent LT were included in this sample."

but further

page 8- "We excluded patients with variceal bleeding within two weeks of listing (in order to exclude TIPS for variceal bleed) for LT and those listed for acute liver failure or hepatocellular carcinoma (HCC)."

Answers: We apologize for repetition of inclusion/exclusion criteria. Please see revised statement about the "study population" on page 8 under the methods section: "After application of exclusion criteria (Figure 1) the analytic sample consisted of 32,783/114,770 (28.5%) patients with ascites who underwent LT and had a known TIPS status. Among these 32,783 patients with ascites, 1,366 patients underwent TIPS while 31,417 patients did not undergo TIPS." Also see figure 1 for visual breakdown of inclusion/exclusion criteria.

Comment: There is inconsistency of data presented in the text and table 1 of the manuscript: page 9 "there were less patients with severe hepatic encephalopathy (HE) in the TIPS group (n=68; 15%) as compared to without TIPS (n=2218; 20%) (p=0.01).

Answer: Thank you for bringing this typographical mistake to our attention. The data in table 1 was accurate. Revised manuscript will read as follows on page 9: "Plausibly, there were less patients with severe hepatic encephalopathy (HE) in the TIPS group (n=68; 4.9%) as compared to without TIPS (n=2218; 7%) (p=0.01)."

Comment: Page 10 – "...is in line with multiple other studies^[9, 12, 14, 17]. These studies also did not find any difference in operative time, transfusion and LOS." but further page 11 "Increased LOS is consistent with previous studies which found that patients who have undergone TIPS have increased transfusion requirements, require longer operative times and have more technical complications during the LT^[9, 16]."

Answer: We agree that the wording of the statement on page 11 was not clear. As a result, page 10 will read as is, but the statement on page 11 is revised: Existing literature on LOS is variable with certain studies describing intra-operative complications in patients who have undergone TIPS^[16]. On the other hand, additional studies have not found TIPS to affect the LOS in post LT setting^[14,20].

Comment: What does it mean hypertension in table 1- portal or arterial ?

Answer: Table 1 has been corrected to specify arterial hypertension.

Comments: All abbreviations should be explained at the time of their first appearance in the text but there is no need to repeat them eg. page 6 "large volume paracentesis (LVP) in controlling refractory ascites with no effect on long-term survival^[1-5]. Several meta-analyses have also compared large volume paracentesis (LVP)"

Answer: We carefully review the paper and explained all abbreviations in full form in text. Second sentence will read LVP alone: "Several meta-analyses have also compared LVP and TIPS in the management of refractory ascites and found TIPS to be more effective in controlling recurrent ascites^[6-8]."

Comment: Tables should be self-explanatory, so their legends should contain all abbreviation explanations (not only ALD, what about MELD, BMI etc.)

Answer: See table for corrections.

Comment: The conclusion "In conclusion, we found that TIPS is not a commonly used intervention for the management of ascites in patients on the waitlist for LT." - It does not reflect the aim of the study.

Answer: Adjusted to read: "In conclusion, we found that TIPS had no effect on the 30-day mortality after LT and the need for re-transplantation. TIPS increased time on LT waitlist while also increasing length of hospital stay. "

Comment: statistics - why the Authors include MELD and liver biochemical parameters that are included in it (bilirubin, creatinine, INR) in the same statistical model of their multivariate analysis ?

Answer: Thank you for pointing out this point. We felt that by including the various components of the MELD score, we could provide more detailed analysis to determine if any one of those components alone could have an individual effect on LT outcomes.

Comment: Last but not least : References should be corrected according to the rules used by the Journal eg. "The New England journal of medicine 2000;.." should be NEJM, 2000 etc.

Answer: Thank you, reference formatting has been corrected.

Comment: Also English language polishing is required.

Answer: Thank you, additional revisions have been made to aim to edit any language or grammatical errors.

Reviewer #3 (02861379):

Comment: The paper is well written and the design is good. However, some Issues should be explicated and clarified. 1. Usually TIPS has some complications. What factors could lead to complications of TIPS? And how to achieve the right situation from TIPS?

Answer: This is a great point that is brought up. Particularly within the scope of our study which focused on LT outcomes, we found that hepatic encephalopathy (HE) contributed to morbidity post-LT such as increased LOS. On page 11 we discuss further: "...HE contributed most to LOS followed by TIPS itself. This finding is remarkable given encephalopathy is a known complication of TIPS^[7, 8]. TIPS insertion may contribute to ongoing encephalopathy and therefore increase length of hospital stay."

However, much value could be found from additional studies looking into the outcome of TIPS itself which likely would require data obtained from sources outside of the UNOS database in addition to data from UNOS.

Once the factors that contribute to TIPS complications are elucidated, the outcomes of TIPS can be improved by limiting these factors.

Comment: Since Liver functional status at baseline was not consistent between two groups TIPS Non group and TIPS Days group at on LT waitlist Non. How to compare within Mortality 30 days and of hospital stay Length?

Answer: This is a very interesting point and I believe requires further investigation in future studies. The higher functional status at listing (lower MELD) among the TIPS group is partly intrinsic as TIPS will only be placed in those patients with lower MELD scores to reduce the morbidity and mortality risk involved with the TIPS procedure itself. However, future studies could create a more homogeneous comparison by only comparing non-TIPS patients with equal MELD scores to their TIPS counter-parts at time of listing. Prospective studies could be especially useful in capturing equivalent groups.

Comment: In addition to MELD, there are also many other prognostic models for evaluating the severity of liver function. Author should add other prognostic models for comparing of the severity of liver function those patients.

Answer: Thank you for this observation. Other prognostic models used to assess severity of liver disease include Child Pugh score and Maddrey score (for only alcoholic liver disease). In order to list patients for liver transplantation, however, the currently approved scoring system used is the MELD score. Therefore, we used MELD score in our population listed for liver transplantation.

Reviewer #4 (03294162):

Comment: The article is very well described; it was properly planned and conducted. However, it has some shortcomings that need to be addressed and include the following: Major: 1- We found all the problems related to retrospective studies using large databases. There are no more details of the case, and sometimes these data are important. As in the case of the study the indicating the TIPS. 2- The authors included in the study only patients who placed TIPS after inclusion on the waiting list for liver transplantation. 3- The indication of TIPS isn't specified in retrospective database. Thus, the authors ruled out only patients with variceal bleeding within two weeks of listing. This information would be important to assess the impact of TIPS in the post-transplant. 4- The increased hospital stay is probably due to the fact that higher MELD, and not due to TIPS 5- There were no reported complications related to TIPS 6- The authors discuss the results findings in results section

Answer: We agree with your comments regarding limitations of a retrospective study based on a large database. In an attempt to keep our study group homogeneous, patients undergoing TIPS for variceal bleeding were excluded. Patients without ascites and with acute liver failure were excluded. We attempted with the inclusion/exclusion criteria to limit our study group to those undergoing TIPS for ascites.

Answer to your comment regarding "increased hospital stay with TIPS may actually be a result of higher MELD score/more advanced liver disease in that cohort" is included on page 11 under discussion section: "Among other predictors of increased LOS were advanced age, high MELD score and CIT. All these factors are recognized predictors of increased LOS and reported in literature^[18, 19]. Of note, the TIPS group in our study began with a lower MELD score at the time of listing but had higher MELD scores at the time of LT. This finding suggests patients undergoing TIPS were able to survive longer on the wait list with continued progression of liver disease at the time of LT. More advanced disease among TIPS patients would explain increased LOS post-LT."

Answer: You inquired about the complications related to TIPS. Unfortunately, specific complications related to TIPS such as migration of TIPS, requirement for blood transfusion, etc are not part of UNOS database; therefore, they could not be

included in this study. However, major short term complications such as mortality, graft failure requiring re-liver transplantation were included in this analysis. One of indirect measure of TIPS related complication is LOS and it was also part of our study.

Answer: Discussing results findings in the results section: Thank you for your comment. We have included results findings in both the results section as well as in the attached tables. Further discussion of the results findings and their significance can be found in the discussion section.