

Manuscript ID: 54353

Title: Transjugular intrahepatic portosystemic shunt for pyrrolizidine alkaloid-related hepatic sinusoidal obstruction syndrome

Journal: World Journal of Gastroenterology

Response to Reviewers' comments

Dear Editor,

We thank you for your careful consideration of our manuscript. We appreciate your response and overall positive initial feedback and made modifications to improve the manuscript. After carefully reviewing the comments made by the Reviewers, we have modified the manuscript to improve the presentation of our results and their discussion, therefore providing a complete context for the research that may be of interest to your readers.

We hope that you will find the revised paper suitable for publication, and we look forward to contributing to your journal. Please do not hesitate to contact us with other questions or concerns regarding the manuscript.

Best regards,
Weifu Lv

Round 1

Reviewer #1

Abstract

Method section stated this is a retrospective study. However, later sentence stated that patients were assigned to TIPS and conservative management group. If this is a retrospective study, how can we assign patient's treatment arm?

Response: We thank the Reviewer for the comment. The statement was edited to: "Patients were divided into the TIPS and conservative treatment groups according to the therapy they received."

Results section stated that maximal ascites depth was significantly lower on TIPS group. At our institution, we usually do paracentesis if the patient has ascites and undergoing TIPS. Is this a confounding factor?

Response: We thank the Reviewer. In the study, ascites drainage was only considered if the patient has obvious symptoms of abdominal distension. In the TIPS group, after the operation, the ascites subsided, and no patients were treated with ascites drainage. In the conservative treatment group, even if ascites drainage were performed, it is only for symptom relief without managing the cause of ascites. There is no room to add this to the Abstract, but it was added to the main text.

Last sentence. "time after surgery" should be phrased as "time after TIPS placement"

Response: We agree with the Reviewer. It was edited accordingly.

Introduction: One sentence stated that TIPS is not a recommended treatment in current guideline. This appear to be EU based guideline which is likely related to bone marrow transplantation related SOS. Earlier sentences emphasized the differences between PA-HSOS and HSCT-HSOS. Is this an appropriate use of reference?

Response: We thank the Reviewer for the comment. This was revised.

Methods: Methods sections were well written. No concerns here.

Response: We thank the Reviewer.

Results: TIPS group had about the double the number of patients on the conservative treatment group. As methods section stated that those who underwent the conservative treatment refused TIPS placement. I am not sure if this had some selection bias or put this study at risk for potential confounders.

Response: We understand and agree with the Reviewer's concerns. This was a retrospective study, and we had to analyze the patients according to the treatment they received. This is an inherent bias to retrospective studies. In this study, conservative treatment was undertaken in patients who had failed conservative treatment for 2

weeks or who had refused TIPS treatment for ascites and jaundice during treatment. Since the patients with effective conservative treatment were not included in this study, the sample size of the conservative treatment group was small, and there was indeed a bias. Nevertheless, the preoperative baseline level of the two groups was basically the same, which reduced the bias to some extent. This was added to the Limitations.

My other concern is that much higher mortality on conservative treatment group. Were they too sick to get TIPS, and this made the mortality difference?

Response: We thank the Reviewer for the comment. The preoperative baseline characteristics of the two groups were similar, and the conservative group at baseline did not show more severe conditions. In addition, most of the patients in the conservative group died by 1-6 months after the conservative treatment, and the main causes of death were infection, liver failure, and multiple organ failure. We consider that this was due to the aggravation of the disease rather than the severity of the underlying disease.

Discussion: Mortality appears similar to previously published study. This may suggest generalizability of this study. It may not be appropriate to compare overall mortality for HSCT-HSOS to PA-HSOS as overall mortality from HSCT-HSOS may be coming from bone marrow related issues.

Response: We agree with the Reviewer. This was revised.

It would be helpful for the readers to know why the 2 patients in TIPS group died. Is this procedure related complication? I can only see one of them.

Response: We thank the Reviewer for the comment. Two patients in the TIPS group died, and none of them had any complications like iatrogenic hemorrhage or hepatic encephalopathy. One patient with preoperative bilirubin of 380 $\mu\text{mol/l}$ died of liver failure 1 week after surgery. Another patient with bilirubin at 84 $\mu\text{mol/l}$ before surgery developed a severe pulmonary infection on the third day after surgery and died of respiratory failure. This was added to the Results.

Figure Attached image has low resolution which was hard to interpret. Please provide figure with better resolution for Kaplan-Meier survival curve.

Response: We are sorry for this. We now provide a better image.

Overall comments

This is a well written manuscript on the topic which appear to be more common in China. This study may provide importance of TIPS in patients with PA-HSOS. However, future RTC is needed to confirm this findings.

Response: We thank the Reviewer for taking the time to review our manuscript and for the useful comments.

Round 2

First, this study may provide importance of TIPS placement in patients with for pyrrolidine alkaloid-related hepatic sinusoidal obstruction syndrome (PA-HSOS). Second, this is a retrospective study, so we cannot conclude cause effect model, however this showed promising data on positive benefit of TIPS placement in PA-HSOS. As sinusoidal obstruction syndrome is more common in bone marrow transplant recipient, currently there is limited evidence on PA-HSOS treatment options. Third, as this is a retrospective study, future RTC is needed to confirm this findings as this study has potential bias. Other comments: I see the improvement from the original manuscript, and I appreciate an effort. It is minor, but I think core tip should include design or method of the study as I only see the result. If I only looked at core tip, I do not understand what kind of study was conducted. After correcting this, I think it would be appropriate to accept the manuscript.

Response: We thank the Reviewer for the comment.