**ROUND 1**

**Response to the Reviewers' Comments**

Journal: World Journal of Gastroenterology (Manuscript ID: 86784)

Title: "Impressive recompensation in transjugular intrahepatic portosystemic shunt-treated individuals with complications of decompensated cirrhosis based on Baveno VII criteria"

Dear editor,

Thank you very much for your letter with reviewers' comments. These suggestions are very helpful for us to improve the quality of the manuscript. We have revised the manuscript in accordance with the suggestions from the editor and the reviewers. Also, we have updated supplementary material and renumbered them to better support our results. For your rapid check, we list below the reply to the reviewers' comments point by point. And all changes made in the revised manuscript have been highlighted with yellow color. We greatly appreciate for the valuable comments from the editor and reviewers, which help us to improve the quality of this paper. Moreover, we would like to express our thanks for your processing the reviewing processes. I hope you will find this revised manuscript acceptable for publication in World Journal of Gastroenterology.

Sincerely,

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## Response to Reviewers' Comments

For Reviewer #1:

*Comments: It is an interesting study about liver recompensation after TIPS insertion. The authors retrospectively investigated the effect of TIPS, at 1 year after the insertion. While the results are important, i have a major concern. Though all patients had received treatment against the causative factor of liver cirrhosis and afterwards they underwent TIPS, it is difficult to clarify whether liver recompensation in the 1 year of follow up period had occured due to the reduction of portal hypertension because of TIPS as the authors declare, or due to the elimination of the causative factor which was responsible for the liver damage. A possible suggestion would be to investigate separately those patients who had complete and sustained elimination of the causative factor plus TIPS, in comparison to patients who had been treated but they had not achieved complete and sustained response against the causative factor plus TIPS. I believe that this issue needs further validation.*

*Q1: In the section of results (page 8), you did not give the mean value of ALT but the median one. Please correct.*

**Response**: Thank you for your carefully review. Before doing data analysis, we always perform a normality test first. The results that conformed to the normal distribution were expressed as mean ± standard deviation, while the results that did not conform to the normal distribution were expressed as the mean and interquartile range. This was a scientific expression that conforms to statistics, not a wrong wording. Therefore, I was pretty sure that I was writing correctly. However, I did appreciate your careful work. Hope our explain did make sense to reassure you.

*Q2: You found a decrease of PPG postoperatively after the insertion of TIPS. Please clarify the exact time that the PPG was measured postoperatively.*

**Response:** Thank you for your professional review. In our institute, PPG was routinely measured before and after TIPS insertion. More specifically, postoperative PPG referred to the immediate PPG right after TIPS insertion. But we also known, the portal pressure gradient (PPG) measured at the time of TIPS completion (immediate PPG) was easily disturbed by many factors. Moreover, recent study had suggested that delayed PPG (2-4 days after TIPS) had higher predictive power for variceal rebleeding than immediate PPG [1]. However, delayed PPG was not routinely performed at our center. We really hoped our explanations were acceptable.

*Q3: You mentioned in page 9 that "Patients were divided into a recompensation group (n = 20) and a no recompensation group (n = 44), of which 31% met the definition of recompensation to compare their baseline variables.". What do you mean? It is a little bit confusing. How patients without recompensation had met the definition of recompensation?*

**Response:** Thank you for your carefully review. Literally, our previous expression

was indeed ambiguous and thus we made the appropriate modifications. Please check the revised version which was highlighted in yellow. Hope our fix clears up your confusion.

*Q4: Patients who achieved recompensation returned to Child-Pugh A stages in higher proportions. Obviously, figure 4 is wrong. Sceme D probably represents patients with recompensation and E those without, not the opposite. Please correct.*
**Response:** Thank you for your carefully review. Sorry again for our carelessness and we had corrected figure 4 legend in the revised version.

*Q5: In the multivariate analysis, the baseline Child-Pugh score and MELD score were not found to independently associate with liver recompensation at 1 year after the TIPS implementation. I believe that this is probably because of the small number of patients included in the study. Please discuss it more extensively in the section of discussion*
**Response:** Thank you for your professional suggestion and we had expanded the relevant content in the section of discussion in the revised manuscript, which were highlighted in yellow.

For Reviewer #2:

*Comments: I congratulate the authors for conducting this very relevant study which may have a potential future bearing in our practice while taking care of decompensated chronic liver disease patients. They showed that around one-third of individuals achieved recompensation after TIPS and also determined that preoperative PPG < 12 mmHg and a younger age were independent predictors of recompensation. The quality of data and discussion is in general good and has been supplemented with appropriate discussion and reasoning. While we can appreciate the many strengths of the study, we must also look into the limitations: - retrospective nature and a small single centre data limits the generalizability of the study. A validation cohort might have helped to confirm the independent association of preoperative PPG < 12 mmHg and a younger age with recompensation. Further, the Baveno VII definition of recompensation is yet not validated across different races and across different aetiologies of cirrhosis and hence using the same may not be appropriate.*

*Q1. The Helsinki declaration has been recently amended in 2013. State whether your study conforms to the same.*
**Response**: Thank you for your carefully review. Our study did conform to the 2013 Declaration of Helsinki and we have corrected the writing in the revised manuscript.

*Q2. In the result sections, in the paragraph on Baseline and on-treatment characteristics of patients with and without recompensation, what does the author mean by "Patients were divided into a recompensation group (n = 20) and a no*

*recompensation group (n = 44), of which 31% met the definition of recompensation [7,8] to compare their baseline variables." Did 31% of patients without recompensation also meet some criteria of recompensation?*

**Response**: Thank you for your careful reading of our manuscript. Literally, our previous expression was indeed ambiguous and thus we made the appropriate modifications. Please check the revised version which was highlighted in yellow. Hope our fix clears up your confusion.

## REFERENCES

1. Ma L, Ma J, Zhang W, Liu Q, Zhang Z, Yang M, Yu J, Zhou X, Chen S, Wang J, Luo J, Yan Z. Predictive power of portal pressure gradient remeasured shortly after transjugular intrahepatic portosystemic shunt. Hepatol Int. 2023 Apr;17(2):417-426.

**ROUND 2**

**Response to the Reviewers' Comments**

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Dear editor,

Thank you very much for your letter with reviewers' comments. We have made a point-to-point response to the review comments. We greatly appreciate for the valuable comments from the reviewers, which help us to improve the quality of this paper. Moreover, we would like to express our thanks for your processing the reviewing processes. I hope you will find this manuscript acceptable for publication in World Journal of Gastroenterology.

Sincerely,

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## Response to Reviewers' Comments

*SPECIFIC COMMENTS TO AUTHORS*

*The authors answered to my comments and corrected the errors that i had mentioned. However, they did not answer to my major concern about the methology of the study. As it is a single arm study, and all of patients had received treatment against the causative factor of liver cirrhosis and afterwards they underwent TIPS, it is difficult to clarify whether liver recompensation in the 1 year of follow up period occured due to the reduction of portal hypertension because of TIPS, as the authors declare, or due to the elimination of the causative factor which was responsible for the liver damage. The basic problem of the study is the absence of a control group. A group composed only with patients who had received the standard of care treatment (treatment against the causative factor of the liver damage merely, without TIPS). This is a major limitation of the study and of great importance. I am not sure if this can be overpassed. The authors should discuss this further in the discussion. Moreover, they must describe extensively those factors or data that make them believe that the insertion of TIPS contributed to the liver recompensation more than the elimination of the causative factor itself.*

**Response**: Sorry for our oversight on your major concern. As we all known, TIPS is an effective strategy on complications of portal hypertension, such as refractory ascites and variceal bleeding. Currently, the effect of TIPS on liver recompensation is unknown. In this study, we found the TIPS can contribute to recompensation based on previous recompensation definition.

The reasons that the insertion of TIPS contributed to the liver recompensation more than the elimination of causative factor itself is as follow: (1) Based on the population characteristics of this study (decompensation of liver cirrhosis), especially in line with TIPS treatment indications, we have reason to believe that simple etiological treatment is not sufficient to achieve decompensation according to its definition. Furthermore, most patients in this study who had received prolonged causative therapy prior to TIPS still experienced decompensated events, which further confirm the above view. (2) The primary condition for the definition of recompensation is to remove/suppression the disease etiology. If the disease etiology is not treated, although TIPS can improve the patient's prognosis, we cannot make a conclusion that TIPS can recompensate patients with portal hypertension. This is the result of strictly following BAVENO VII's definition of recompensation. (3) Besides, in our previous studies [1,2], we have confirmed that TIPS can improves liver blood supply, volume, and function, which indirectly supports the effectiveness of TIPS operation in liver recovery. However, in this study, we redefined liver recovery as recompensation, based on new concepts. (4) We must emphasize that in addition to patients with decompensated liver cirrhosis, the patients enrolled in this study must also meet the TIPS indications. Although it has been documented that treatment of the etiology alone can lead to recompensation of cirrhosis, the degree of decompensation of

cirrhosis was mild in the patients enrolled in these studies [3,4]. However, in our study, the enrolled patients have already met the TIPS indications, which means that the degree of liver cirrhosis in these patients is already very serious. Therefore, etiological treatment alone is completely insufficient to suppress recurrent fatal complications of portal hypertension, let alone recompensation of cirrhosis. (5) There was no untreated control group for ethical reasons, since etiological treatment (such as antiviral therapy or alcohol abstinence) has become the standard of care. Although scientifically speaking, our research methods are not rigorous. However, in real clinical practice, it is inappropriate to use the etiological treatment or TIPS treatment alone as the control group for patients in line with TIPS indications. In other words, once a patient meets the indications for TIPS, it is unethical to treat the cause alone without TIPS or receive TIPS alone without etiological treatment.

Based on the above considerations, we believe that in this study, the reversal of portal hypertension is the key factor in the recompensation of liver cirrhosis, rather than the etiological treatment. Really hope our explanation makes sense and thanks again for your scientific rigor.

**REFERENCES**

1. Pang N, Zhao C, Li J, Li L, Yang X, Yang M, Wu Z, Feng D. Body mass index changes after transjugular intrahepatic portosystemic shunt in individuals with cirrhosis. Nutrition. 2021 Apr;84:111095. doi: 10.1016/j.nut.2020.111095. Epub 2020 Nov 30. PMID: 33571910.

2. He J, Li J, Fang C, Qiao Y, Feng D. The Relationship and Changes of Liver Blood Supply, Portal Pressure Gradient, and Liver Volume following TIPS in Cirrhosis. Can J Gastroenterol Hepatol. 2022 Dec 8;2022:7476477. doi: 10.1155/2022/7476477. PMID: 36531835; PMCID: PMC9754828.

3. Wang Q, Zhao H, Deng Y, Zheng H, Xiang H, Nan Y, Hu J, Meng Q, Xu X, Fang J, Xu J, Wang X, You H, Pan CQ, Xie W, Jia J. Validation of Baveno VII criteria for recompensation in entecavir-treated patients with hepatitis B-related decompensated cirrhosis. J Hepatol. 2022 Dec;77(6):1564-1572. doi: 10.1016/j.jhep.2022.07.037. Epub 2022 Aug 28. PMID: 36038017.

4. Hofer BS, Simbrunner B, Hartl L, Jachs M, Balcar L, Paternostro R, Schwabl P, Semmler G, Scheiner B, Trauner M, Mandorfer M, Reiberger T. Hepatic recompensation according to Baveno VII criteria is linked to a significant survival benefit in decompensated alcohol-related cirrhosis. Liver Int. 2023 Jul 20. doi: 10.1111/liv.15676. Epub ahead of print. PMID: 37469291.