

## Point-by-point responses to the reviewer's comments

First, we thank the reviewers for their positive and constructive comments and suggestions.

Reviewer #1:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade C (A great deal of language polishing)

**Conclusion:** Major revision

**Specific Comments to Authors:** The authors have provided interesting results and relevant to the present clinical practice.

Major issue with the analysis is that there are differences in the baseline characteristics of the 2 groups as shown in Table 1. The authors should consider propensity score matching for analysis.

**Response:** Thank you very much for your comment. PSM has been considered in the initial stage of the analysis, but if the "nearest" method was selected, 14 patients cannot be included in the study. Meanwhile, the conclusion has not been shaken even if the TIPS group is more serious. Therefore, PSM has not been selected due to the sample size.

My other comments are as follows: 1. Abstract a. In the background of the abstract, the authors state that "it is controversial whether TIPS can improve survival" - multiple studies have demonstrated an improvement in medium to long term survival and improvement in quality of life with TIPS- this statement needs to be revised.

**Response:** Thank you very much for your comment. We have revised the statement.

b. In aims section of abstract the group of patients/indication of TIPSS should be mentioned rather than just "select group"

**Response:** Thank you very much for your comment. We have revised the statement.

c. In methods section of abstract it is not clear whether the patient group had esophageal varices, gastric varices, or both?

**Response:** Thank you very much for your comment. The patients included was cirrhotic patients with esophageal varices and/ or gastric varices.

d. Mention the acronym of OHE.

**Response:** Thank you very much for your comment. We have revised the statement.

e. It is not clear whether the median follow up mentioned is for the whole cohort or equal for both groups (49.5 months)

**Response:** Thank you very much for your comment. We have revised the statement.

2. Introduction a. Line 8 should read “splanchnic vasodilation.”

**Response:** Thank you very much for your comment. We have revised the statement.

b. This line should be clarified or rephrased “to make the varicose veins ischemic and necrotic, there have been some endoscopic treatments for VB thus far.”

**Response:** Thank you very much for your comment. We have revised the statement.

c. This line needs to be corrected “Transjugular intrahepatic portosystemic shunt (TIPS) should be used only for rebleeding patients” as pre-emptive TIPS may also be done to prevent rebleed in high risk patients

**Response:** Thank you very much for your comment. We have revised the statement.

d. Multiple studies have shown survival benefit with TIPS which should be cited here.

**Response:** Thank you very much for your comment. We have added the studies in the INTRODUCTION.

e. Hepatic venous pressure gradient has been shown to predict outcomes in patients with compensated cirrhosis, which should be clarified in paragraph 2

**Response:** Thank you very much for your comment. We have revised the statement.

f. The introduction needs to be revised after adding references cited above.

**Response:** Thank you very much for your comment. We have revised the statement.

3. Methodology a. Methodology of assessment of HVPG should be written in past tense.

**Response:** Thank you very much for your comment. We have revised the statement.

b. Theoretically the identification of occlusion and intrahepatic shunts should be done before assessment of pressure and not after- authors should clarify the methods used.

**Response:** Thank you very much for your comment. We are sorry for confused presentation. We have revised the statement.

c. It is not clear from the methodology if all patients underwent variceal banding prior to TIPS.

**Response:** Thank you very much for your comment. We are sorry for confused presentation. In our study, patients with EVL before TIPS were excluded. We have revised the statement.

d. The standard medical care and resuscitation provided prior to the HVPG assessment and endotherapy is not mentioned.

**Response:** Thank you very much for your comment. We are sorry for confused presentation. In our study, patients included was clinically-stable cirrhotic patients. All patients included underwent preoperative examination to rule out contraindications of HVPG measurement and then received HVPG measurement. We have revised the statement.

e. It is not clear what the management protocol was for patients who had active bleeding from esophageal or gastric varices.

**Response:** Thank you very much for your comment. We are sorry for confused presentation. In our study, patients included was clinically-stable cirrhotic patients. We have revised the statement.

f. A major limitation here is that the adherence to a post endotherapy schedule of variceal obliteration is not mentioned. If complete obliteration is not achieved, this would affect rebleeding rates and therefore survival.

**Response:** Thank you very much for your comment. In our exclusion criteria, patients without sequential endoscopic therapy were excluded.

*The exclusion criteria of the study were as follows: (1) sequential endoscopic therapy was not standardized;*

g. Provide objective markers for assessment of tolerance of beta blockers

**Response:** Thank you very much for your comment. We have added the statement in the supplemental materials.

h. Mean doses of carvedilol and propranolol should be mentioned along with those who discontinued therapy with reasons

**Response:** Thank you very much for your comment. We have added the statement in the supplemental materials.

i. How was the decision to give a patient carvedilol as opposed to propranolol decided? Carvedilol is not an NSBB and provides additional survival benefits- would this make an impact on the results?

**Response:** Thank you very much for your comment. This retrospective study was conducted from 2013 to 2019. Previous guidelines recommended propranolol as the preferred NSBBs. With the change of guidelines, carvedilol is now preferred as the preferred oral portal hypertensive agent. A review containing 10 studies showed no clear beneficial or harmful effects of carvedilol versus traditional.

[1]Zacharias AP, Jeyaraj R, Hobolth L, Bendtsen F, Gluud LL, Morgan MY. Carvedilol versus traditional, non-selective beta-blockers for adults with cirrhosis and gastroesophageal varices. *Cochrane Database Syst Rev.* 2018 Oct 29;10(10):CD011510. doi: 10.1002/14651858.CD011510.pub2. PMID: 30372514; PMCID: PMC6517039.

j. Clarify the timepoints at which rebleeding was assessed (42-days/1-year/longer)

**Response:** Thank you very much for your comment. When the patient experienced hematemesis or black stool again after treatment, the patient contacted our follow-up nurses for re-hospitalization and hemostasis. Rebleeding does not require time point evaluation.

*Any patients with complications during the follow-up were admitted to the hospital for active treatment.*

k. Were all patients who underwent TIPSS started on anti-encephalopathy measures such as lactulose or rifaximin?

**Response:** Thank you very much for your comment. Patients accepting TIPS in our center took lactulose orally for 1 month after TIPS, and were told to maintain bowel movements 2-3 times a day and take lactulose orally as needed at the follow-up site . Rifaximin was evaluated on the basis of plasma ammonia results on the first day after TIPS. If plasma ammonia was higher than the upper limit of normal on the first day after TIPS, rifaximin was usually 200 mg twice a day, and rifaximin usage was adjusted according to the plasma ammonia level at each follow-up site. We have added the statement in the supplemental materials.

4. Results a. Mention the baseline demographic and clinical data of the cohort at baseline.

**Response:** Thank you very much for your comment. The baseline demographic and clinical data of the cohort at baseline are shown in Table 1.

b. In both groups, patients with higher Child score received TIPS- please mention in the discussion how this could impact the results of the study.

**Response:** Thank you very much for your comment. We have added the statement in the Discussion.

c. Please mention in absolute numbers of patients with esophageal/gastric varices along with subtypes of gastric varices rather than in a yes/no format

**Response:** Thank you very much for your comment. We are sorry for confused presentation. We have revised the statement.

d. Subgroup analysis for cardiofundal and esophageal varices should include rebleed rates.

**Response:** Thank you very much for your comment. The subgroup analysis on rebleeding for EV and GOV1 was shown in supplemental figure 2 J K L.

e. There should be a section on the control of etiology (abstinence, antiviral therapy)

**Response:** Thank you very much for your comment. We are sorry for confused presentation. Etiological treatment was followed from beginning to end throughout the study, including antiviral therapy for viral cirrhosis, abstinence therapy for alcoholic cirrhosis, UDCA therapy for PBC, weight loss on a low-fat diet in patients with non-alcoholic fatty cirrhosis and so on. Monitoring was conducted at each follow-up site. We have revised the statement.

f. Authors state "For cirrhotic patients who had etiologies unrelated to viral and alcoholic hepatitis, TIPS did not have a significant transplant-free survival benefit as shown in the Supplemental Figure 1." What fraction of patients were compliant to alcohol abstinence and were on antivirals. Is the benefit in survival due to different therapies or treatment of underlying etiology of cirrhosis. Was etiology included in the multivariate analysis for survival?

**Response:** Thank you very much for your comment. We are sorry for confused presentation. Etiological treatment was followed from beginning to end throughout the study, including antiviral therapy for viral cirrhosis, abstinence therapy for alcoholic cirrhosis, UDCA therapy for PBC, weight loss on a low-fat diet in patients with non-alcoholic fatty cirrhosis and so on. Monitoring was conducted at each follow-up site. We have revised the statement. The etiology was not included in the multivariate analysis for survival.

g. It is not clear what percentage of the study population had cardiofundal varices or esophageal varices.

**Response:** Thank you very much for your comment. The data have been added in Table 1.

h. What is the reason for progressive increase in MELD and MELDNa values after endotherapy or TIPSS? Were alternative therapies like plasmapheresis etc advised for patients with worsening MELD?

**Response:** Thank you very much for your comment. Increasing scores are considered to be associated with the progression of chronic liver disease.

*Any patients with complications during the follow-up were admitted to the hospital for active treatment.*

The therapies after re-hospitalization was decided by the patient based on the professional advice given by the doctors give according to the clinical situation. In fact, during the follow-up period, only 7 patients underwent plasmapheresis.

i. What were the time durations at which stent blockage was detected? How many patients underwent rescue procedure due to obstruction?

**Response:** Thank you very much for your comment. Doppler ultrasound for TIPS-stent was performed at each follow-up site to assess stent patency, and acute stent occlusion occurred in 6 patients between follow-up sites leading to acute decompensation events.

*Stent dysfunction in 6 (66.67%) patients with high-HVPG was discovered due to rebleeding or ascites, while in low level during regular follow-up.*

j. Clarify the statement "There were similar trends shown in the patients without stents (Supplemental Figure 1)."

**Response:** Thank you very much for your comment. A subgroup analysis of hepatic veins without shunt was performed based on the Baveno VII guidelines because some of the patients included had minor shunt. We have revised the statements.

k. Is varicose synonymous to variceal. Use variceal uniformly.

**Response:** Thank you very much for your comment. We are sorry for confused presentation. We have revised the statement.

l. Figure 2 can have either 1 (a) or 1 (b) and either 2 (a) or 2 (b).

**Response:** Thank you very much for your comment. We have revised the Figure 2.

5. Discussion a. The evidence of HVPG stratified approach for treatment is established for compensated cirrhosis with very limited data for decompensated patients. This should be clarified here

**Response:** Thank you very much for your comment. We have added the statement in the Discussion.

b. How was the HVPG cut off value of 16 mm of Hg reached?

**Response:** Thank you very much for your comment.

*It was proved that the lowest pressure associated with continued bleeding or rebleeding was 16mmHg in 1991<sup>[23]</sup>. Furthermore, Ca`ndid V et al pointed out that HVPG >16 mmHg was one of the predictors of the failure of the therapy<sup>[24]</sup>.*

Furthermore, this study was based on our previous study.

[12] Guo H, Zhang F, Yin X, Zhang M, Xiao J, Wang Y, Zhang B, Zhang W, Zou X, Zhuge Y. Endoscopic therapy +  $\beta$ -blocker vs. covered transjugular intrahepatic portosystemic shunt for prevention of variceal rebleeding in cirrhotic patients with hepatic venous pressure gradient  $\geq 16$  mmHg. *Eur J Gastroenterol Hepatol.* 2021 Nov 1;33(11):1427-1435. [PMID: 32868650 DOI: 10.1097/MEG.0000000000001872]

c. Citation 15 is incorrect. Please ensure correct citations

**Response:** Thank you very much for your comment. We are sorry for our mistakes have revised the Figure 2.

d. The cut off of HVPG for 20 mm of Hg is established for compensated cirrhosis and not decompensated cirrhosis- this should be mentioned.

**Response:** Thank you very much for your comment. The cut off of HVPG for 20 mm of Hg is established for AVB-decompensated events. HVPG of >20 mmHg was associated with a significantly longer hospital stay, greater transfusion requirements, and worse survival (1-year mortality: 64% vs. 20%, P<0.002).

[15] Moitinho E, Escorsell A, Bandi JC, Salmerón JM, García-Pagán JC, Rodés J, Bosch J. Prognostic value of early measurements of portal pressure in acute variceal bleeding. *Gastroenterology*. 1999 Sep;117(3):626-31. doi: 10.1016/s0016-5085(99)70455-5. PMID: 10464138.

e. The authors mention that patients undergoing EVL had “partially uncontrolled bleeding”. Please clarify the meaning of this sentence

**Response:** Thank you very much for your comment. We are sorry for the ambiguous statement. We have revised the statement.

f. Authors have not mentioned what are “medium” and “high” HVPG values.

**Response:** Thank you very much for your comment. We are sorry for the ambiguous statement. We have revised the statement.

g. Please mention the definition for “hyperbilirubin syndrome” and provide a reference for the same.

**Response:** Thank you very much for your comment. In the section of Results, we have defined hyperbilirubinemia as Tbil>34μmol/L.

*TIPS did not induce hyperbilirubinemia(Tbil>34μmol/L<sup>[18]</sup>) in low-HVPG level(Figure 5C/5D)*

[18] Sullivan JI, Rockey DC. Diagnosis and evaluation of hyperbilirubinemia. *Curr Opin Gastroenterol*. 2017 May;33(3):164-170. [PMID: 28333690 DOI: 10.1097/MOG.0000000000000354]

h. The relevance of stating HVPG stratification with regards to splenectomy in the context of this study is not clear

**Response:** Thank you very much for your comment. We have deleted the statement.

i. The discussion is largely based on studies done on patients with compensated cirrhosis rather than decompensated patients as in the current study- it should be revised.

**Response:** Thank you very much for your comment.

[22] **Zhang M, Wang G, Zhao L, Wu Z, Zhang W, Zhang C.** Second prophylaxis of variceal bleeding in cirrhotic patients with a high HVPG. *Scand J Gastroenterol.* 2016 Dec;51(12):1502-1506. [PMID: 27379704 DOI: 10.1080/00365521.2016.1193218]

This study included 46 cirrhotic patients with a history of variceal bleeding.

[23] **Ready JB, Robertson AD, Goff JS, Rector WG Jr.** Assessment of the risk of bleeding from esophageal varices by continuous monitoring of portal pressure. *Gastroenterology.* 1991 May;100(5 Pt 1):1403-10. [PMID: 2013385].

This study included 40 patients with bleeding esophageal varices due to alcoholic cirrhosis

[24] **Villanueva C, Piqueras M, Aracil C, Gómez C, López-Balaguer JM, Gonzalez B, Gallego A, Torras X, Soriano G, Sáinz S, Benito S, Balanzó J.** A randomized controlled trial comparing ligation and sclerotherapy as emergency endoscopic treatment added to somatostatin in acute variceal bleeding. *J Hepatol.* 2006 Oct;45(4):560-7. [PMID: 16904224 DOI: 10.1016/j.jhep.2006.05.016]

This study included 179 cirrhotic patients with AVB.

[25] **Paleti S, Nutalapati V, Fathallah J, Jeepalyam S, Rustagi T.** Balloon-Occluded Retrograde Transvenous Obliteration (BRTO) Versus Transjugular Intrahepatic Portosystemic Shunt (TIPS) for Treatment of Gastric Varices Because of Portal Hypertension: A Systematic Review and Meta-Analysis. *J Clin Gastroenterol.* 2020 Aug;54(7):655-660. [PMID: 31688366 DOI: 10.1097/MCG.0000000000001275]

A review compared BRTO with TIPS in gastric variceal bleeding.

[26] **Stanley AJ, Jalan R, Ireland HM, Redhead DN, Bouchier IA, Hayes PC.** A comparison between gastric and oesophageal variceal haemorrhage treated with transjugular intrahepatic portosystemic stent shunt (TIPSS). *Aliment Pharmacol Ther.* 1997 Feb;11(1):171-6. [PMID: 9042990 DOI: 10.1046/j.1365-2036.1997.106277000.x]

This study included 106 consecutive cirrhotic patients with variceal bleeding (EV/GV)

A comparison of baseline clinical characteristics should be provided.

**Response:** Thank you very much for your comment. The baseline clinical data of the cohort are shown in Table 1.



Reviewer #2:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade A (Priority publishing)

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:** This is a well-written manuscript on a subject of interest. Background and Methods are comprehensive, Results and Discussion are well aligned. I consider this a manuscript of importance to the field. I have no significant remarks.

**Response:** Thank you very much for your comment.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: I have studied carefully the manuscript entitled "Pre-TIPS measurement of hepatic venous pressure gradient and its clinical application: a comparison study: by Wang X et al. The manuscript aims to clinically evaluate the ability of Transjugular Intrahepatic Portosystemic Shunt (TIPS) to improve survival based on pre-treatment measurement of the hepatic-venous-pressure-gradient (HVPG). The title of the manuscript does reflect the main subject. The abstract summarizes effectively the work described in the manuscript. The key words are proper in reflecting the focus of the manuscript. The "Introduction" section adequately describes the background, present status and significance of the study. Methods are quite clearly described, and results are properly presented; however, the research objectives had been partly achieved by the experiments used in this study due to methodological issues (see comments below), while the information provided is not novel (see the recently published paper by Yao Y et al: Hepatic venous pressure gradient (HVPG) predicts liver failure after transjugular intrahepatic portal shunt: a retrospective cohort study. *Ann Transl Med.* 2022 Oct;10(20):1122. doi: 10.21037/atm-22-4737. PMID: 36388791). Discussion should therefore incorporate all useful information derived from the former publication, and further interpret the findings and highlight the key points properly in order to ensure clinical meaningfulness. Illustrations and tables are in general properly prepared. Concerning Biostatistics, there are no apparent errors. Research methods and reporting, as well as ethics statements are proper. Before considering publication, please find below some queries/comments addressed.

Major comments 1) It would be interesting to consider using HVPG as a scale variable rather than a binary one on the basis of a pre-defined cutoff (16mmHg). This approach is awaited to increase statistical power and to contribute to the construction of more effective multivariate models. Furthermore, this approach would enable analysis of all patients as a single group, within which the two offered treatment options (Endoscopic therapy+NSBBs and TIPS) could be evaluated as the independent variable of Cox regression multivariate models incorporating HVPG as a scale variable, as well as any other potential confounding factor, as assessed by univariate analysis.

**Response:** Thank you very much for your comment. In the stage of statistical analysis, we tried to use specific HVPG values to conduct COX analysis, but the results were not ideal, the results of single factor analysis were not satisfactory. However, the binary variable grouping according to the HVPG value was meaningful. It is suggested that the change of HVPG value in a certain range is not enough to affect the prognosis of survival.

2) As the idea is not novel, please discuss the findings of the relevant, recently published paper by Yao Y et al. Hepatic venous pressure gradient (HVPG) predicts liver failure after transjugular intrahepatic portal shunt: a retrospective cohort study. *Ann Transl Med.* 2022 Oct;10(20):1122. doi: 10.21037/atm-22-4737. PMID: 36388791.

**Response:** Thank you very much for your comment. We have read this article carefully and have added this article in the section of Reference.

Minor comments 1) Page 3, "Methods" paragraph, line 5: Please define "OHE" as "overt hepatic encephalopathy".

**Response:** Thank you very much for your comment. We have revised the statement.

2) Page 4, line 6: Please consider amending "ignoring the" for "independently of".

**Response:** Thank you very much for your comment. We have revised the statement.

3) Page 5. line 2nd from bottom: Please amend "During" for "during".

**Response:** Thank you very much for your comment. We have revised the statement.

4) Page 6, "Materials and Methods" section, "Study Design And Patients" paragraph, line 6: Consider using HVPG as a scale variable.

**Response:** Thank you very much for your comment. We have revised the statement.

5) Page 8, "Materials and Methods" section, "Therapy" paragraph, line 4: A significant bias has been introduced due to the fact that the final treatment was decided by the patients. Please discuss in the "Limitations" paragraph of the "Discussion" section.

**Response:** Thank you very much for your comment. We have added the statement.

6) Page 9, "Materials and Methods" section, "Statistical analysis" paragraph, line 9: Please amend "univariable" for "univariate".

**Response:** Thank you very much for your comment. We have revised the statement.

7) Page 9, "Materials and Methods" section, "Statistical analysis" paragraph, lines 9, 11: Please amend "multivariable" for "multivariate".

**Response:** Thank you very much for your comment. We have revised the statement.

8) Discuss the potential clinical meaning of a novel cutoff for HVPG, if such would arise from multivariate analysis, in the context of previously obtained knowledge on the filed.

**Response:** Thank you very much for your comment. We discussed the value of this cut-off in conclusion.

*The use of covered TIPS increases the long-term transplant-free survival in patients with HVPG  $\geq 16$  mmHg who are admitted with variceal bleeding in the long term, while the advantage may not be observed in patients with  $10 \text{ mmHg} \leq \text{HVPG} < 16 \text{ mmHg}$ . Management and treatment of cirrhotic patients becomes more appropriate according to pre-TIPS HVPG measurement.*



## Point-by-point responses to the editor's comments

First, we thank all editors for their positive and constructive comments and suggestions.

(1) Science editor:

The manuscript has been peer-reviewed, and it's ready for the first decision.

Language Quality: Grade A (Priority publishing)

Scientific Quality: Grade B (Very good)

(2) Company editor-in-chief:

作者提供的伦理委员会批准文件尚未签章。请补签章。或将会拒绝手稿。

**Response:** Thank you very much for your comment. We are sorry for misunderstanding the required document. We have reuploaded the **Ethical consent letter** (伦理同意函).

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...".

**Response:** Thank you very much for your comment. We have revised the statements.

Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.

**Response:** Thank you very much for your comment. We have revised the figures.

Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

**Response:** Thank you very much for your comment. We have revised the tables.

Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

**Response:** Thank you very much for your comment. We have revised the figures.

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/>.