

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 82927

Title: Pre-transjugular-intrahepatic-portosystemic-shunt measurement of hepatic venous pressure gradient and its clinical application: A comparison study

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05430684

Position: Peer Reviewer

Academic degree: MD, MSc, PhD

Professional title: Consultant Physician-Scientist, Research Fellow

Reviewer's Country/Territory: Greece

Author's Country/Territory: China

Manuscript submission date: 2023-01-03

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-01-25 20:05

Reviewer performed review: 2023-01-26 19:16

Review time: 23 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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. 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. Minor comments 1) Page 3, "Methods" paragraph, line 5: Please define "OHE" as "overt hepatic encephalopathy". 2) Page 4, line 6: Please consider amending "ignoring the" for "independently of". 3) Page 5. line 2nd from bottom: Please amend "During" for "during". 4) Page 6, "Materials and Methods" section, "Study Design And Patients" paragraph, line 6: Consider using HVPG as a scale variable. 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. 6) Page 9, "Materials and Methods" section, "Statistical analysis" paragraph, line 9: Please

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

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04090502

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Academic Research, Doctor, Postdoctoral Fellow, Research Scientist, Senior Researcher, Staff Physician

Reviewer's Country/Territory: Brazil

Author's Country/Territory: China

Manuscript submission date: 2023-01-03

Reviewer chosen by: Dong-Mei Wang

Reviewer accepted review: 2023-02-15 12:27

Reviewer performed review: 2023-02-25 19:07

Review time: 10 Days and 6 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty

Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation
Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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.

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05122201

Position: Peer Reviewer

Academic degree: DNB, MD

Professional title: Additional Professor

Reviewer's Country/Territory: India

Author's Country/Territory: China

Manuscript submission date: 2023-01-03

Reviewer chosen by: Dong-Mei Wang

Reviewer accepted review: 2023-02-19 03:15

Reviewer performed review: 2023-02-28 03:48

Review time: 9 Days

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
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Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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. My other comments are as follows:

- Abstract
 - 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.
 - In aims section of abstract the group of patients/indication of TIPSS should be mentioned rather than just “select group”
 - In methods section of abstract it is not clear whether the patient group had esophageal varices, gastric varices, or both?
 - Mention the acronym of OHE
 - It is not clear whether the median follow up mentioned is for the whole cohort or equal for both groups (49.5 months)
- Introduction
 - Line 8 should read “splanchnic vasodilation.”
 - 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.”
 - 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 d. Multiple studies have shown survival benefit with TIPS which should be cited here. e. Hepatic venous pressure gradient has been shown to predict outcomes in patients with compensated cirrhosis, which should be clarified in paragraph 2 f. The introduction needs to be revised after adding references cited above. 3. Methodology a. Methodology of assessment of HVPG should be written in past tense. 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. c. It is not clear from the methodology if all patients underwent variceal banding prior to TIPS. d. The standard medical care and resuscitation provided prior to the HVPG assessment and endotherapy is not mentioned. e. It is not clear what the management protocol was for patients who had active bleeding from esophageal or gastric varices. 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. g. Provide objective markers for assessment of tolerance of beta blockers h. Mean doses of carvedilol and propranolol should be mentioned along with those who discontinued therapy with reasons 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? j. Clarify the timepoints at which rebleeding was assessed (42-days/1-year/longer) k. Were all patients who underwent TIPSS started on anti-encephalopathy measures such as lactulose or rifaximin? 4. Results a. Mention the baseline demographic and clinical data of the cohort at baseline 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. 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 d. Subgroup analysis for cardiofundal and esophageal varices should include rebleed rates. e. There should be a section on the control of etiology (abstinence, antiviral therapy) 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? g. It is not clear what percentage of the study population had cardiofundal varices or esophageal varices 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? i. What were the time durations at which stent blockage was detected? How many patients underwent rescue procedure due to obstruction? j. Clarify the statement "There were similar trends shown in the patients without stents (Supplemental Figure 1)." k. Is varicose synonymous to variceal. Use variceal uniformly. l. Figure 2 can have either 1 (a) or 1 (b) and either 2 (a) or 2 (b). 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 b. How was the HVPG cut off value of 16 mm of Hg reached? c. Citation 15 is incorrect. Please ensure correct citations d. The cut off of HVPG for 20 mm of Hg is established for compensated cirrhosis and not decompensated cirrhosis- this should be mentioned. e. The authors mention that patients undergoing EVL had "partially uncontrolled bleeding". Please clarify the meaning of this sentence f. Authors have not mentioned what are "medium" and "high" HVPG values. g. Please mention the definition for "hyperbilirubin syndrome" and provide a reference for the same. h. The

relevance of stating HVPG stratification with regards to splenectomy in the context of this study is not clear 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. A comparison of baseline clinical characteristics should be provided.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Manuscript NO: 82927

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05430684

Position: Peer Reviewer

Academic degree: MD, MSc, PhD

Professional title: Consultant Physician-Scientist, Research Fellow

Reviewer's Country/Territory: Greece

Author's Country/Territory: China

Manuscript submission date: 2023-01-03

Reviewer chosen by: Kai-Le Chang

Reviewer accepted review: 2023-03-22 06:32

Reviewer performed review: 2023-03-22 07:45

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [☒] Yes [☐] No

SPECIFIC COMMENTS TO AUTHORS

I have studied the revised version of the manuscript entitled "Pre-transjugular-intrahepatic-portosystemic-shunt measurement of hepatic venous pressure gradient and its clinical application: A comparison study" by Wang X. et al. The authors have adequately responded to all queries raised by the reviewers and performed the necessary modifications in the text. Hence, the quality of the manuscript has been significantly ameliorated and conveys a clear-cut message to the reader. Under these circumstances, the manuscript could merit publication.