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Title: Comparison of Hepatic Venous Pressure Gradient and Endoscopic Grading of Esophageal Varices

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Responses

Dear reviewers and editors,

We appreciate of your critical reading of this manuscript and detailed comments. We have carefully reviewed the manuscript and revise it according to your comments and recommendations. Details are listed below.

Reviewer 1 (02824224)

Interesting study about correlation between hepatic venous pressure gradient and its clinical manifestation of grade of esophageal varices. Elegant statistical analysis but not many graphics. My congratulations

Responses: We appreciate of your careful reading and we are grateful to get the great comments of our manuscript. The language editing for the revised manuscript was done according to your recommendation.

Reviewer 2 (02486710)

I congratulate the authors for their study. Please see my comments below.

1) Is there any selection bias between the study groups? Can you please present patient characteristics regarding their comorbid factors and their disease severity at the time of measurement?

Responses: Thank you for your careful advice. We documented patient characteristics and performed additional analyses of patient characteristics and evaluated whether it had relationship with hepatic venous pressure gradient (HVPG). Hemodynamic status including heart rate, systemic blood pressure (systolic and diastolic blood pressure), the etiology of liver cirrhosis, sex and presence of comorbid factor showed no relationship with HVPG, except for presence of pre-existing HCC.

2) Any complications developed due to both hepatic venous pressure gradient measurement techniques?

Responses: HVPG measurement is a relatively safe procedure and only minor complications such as hematoma or swelling at the puncture site have been reported. In this study, the technical success rate is 100% in all cases and no procedure-related complication.

3) Correlation between the hepatic venous pressure gradient and the endoscopic grade of esophageal varices is known please describe the novelty of your paper, which was comparing two different technique to measure it.

Response: Thank you for pointing out the novelty of this manuscript. We added the description of the novelty of this study as follow: *This study showed the use and comparison of two different measurement methods of HVPG and showed that the balloon catheter method had better correlation with esophageal varix grading based upon endoscopic findings.*

4) What are the advantages and disadvantages of EH-HVPG and B-HVPG compared to each other in patients esophageal varices?

Response: The balloon tipped catheter is preferred method for HVPG measurement, because it allows serial measurements of free hepatic venous pressure (FHVP) and wedged hepatic venous pressure (WHVP) using the same catheter, inflated and deflated repeatedly. Balloon technique also avoids the decompression effect of venous-to-venous shunts that are proximal to the balloon. When using the end-hole catheter, the WHVP is measured at the level of a small hepatic venule. Because of the heterogeneity of sinusoidal involvement in liver cirrhosis, measurement with end-hole catheter may lead to differences in values when the catheter is wedged in different hepatic veins. On the other hand, the balloon catheter allows measurement in the hepatic veins at the lobar and sublobar levels. This measurement is an average of pressures in several segments of the liver and thus is likely to more closely represent the true portal venous pressure.

5) Can the hepatic venous pressure gradient be measured non-invasively?

Response: There is no reported method to measure hepatic venous pressure non-invasively. Although imaging techniques are very useful for identifying the causes of portal hypertension, no imaging technique has proved sufficiently accurate to replace HVPG measurement, which remains the gold standard for identifying and grading sinusoidal portal hypertension. HVPG measurement is closely correlated with portal pressure gradient and a relatively safe procedure as compared with the direct portal pressure measurement, such as splenic pulp puncture and

percutaneous transhepatic approach. Thus, indirect measurement by using wedged hepatic venous pressure had been used as an alternative way to estimate portal vein pressure.

6) Please re-design your discussion start with concise statement of principal findings; then Strengths and weaknesses of the study; Strengths and weaknesses of the study in relation to other studies, discussing particularly any differences in results; Meaning of the study: possible mechanisms and implications for clinicians ;Unanswered questions and future research. Hope my comments help out respectfully

Response: We appreciate for the detailed suggestion and comments. We re-designed discussion of the manuscript according to your recommendation. Please check the details with the re-submitted manuscript.

Reviewer 3 (00032726)

This study confirmed the correlation between hepatic venous pressure gradient (HVPG) and the endoscopic grade of esophageal varices with related clinical data of 146 patients. The authors concluded that HVPG is positive related with the variceal size as well as the risk of variceal bleeding. The major advantage of this study is the use and comparison of two measurements of hepatic venous pressure. This is a interesting study which will be useful to clinicians in this field. However, there are several questions should be addressed before further consideration.

1) The inclusion criteria should be listed in the text. For instance, cardiovascular diseases can significantly influence the baseline value of blood pressure and patients with these diseases should be eliminated.

Response: We agree with the reviewer that the inclusion criteria should be listed in the text. We listed inclusion criteria that clarify the subjects of the study in the revised manuscript: *Inclusion criteria for the study were: diagnosis of cirrhosis (based on clinical, serological and imaging findings including abdominal computed tomography and/or ultrasound); stable hemodynamic state with no active variceal bleeding at the time of HVPG measurement and no large amount of ascites that might affect intra-abdominal pressure.*

2) The sample size of male patients is two times bigger than that of female patients. Since the average blood pressure of men is higher than that of women the gender difference may causing bias. It is recommended to analyze the data of male and female patients separately.

Response: Thank you for pointing out the possible bias. We performed additional analysis whether the gender difference has relationship with hepatic

venous pressure gradient (HVPG). The analysis showed that there was no significant difference in EH-HVPG ($P = .40$) and B-HVPG ($P = .32$) between the male and female patients.

3) The imaging diagnosis can be influenced by the experience of physicians. Therefore the endoscopic grading of esophageal varices should be made by at least two physicians who have equal experience.

Response: In this study, endoscopic grading of esophageal varices for each case was done by two board-certificated gastroenterologists with 2 and 10 years of experience. We agree with the reviewer that the imaging diagnosis can be influenced by the experience of physicians, however, they performed grading based on the published standard; "The General rules for recording endoscopic findings of esophageal varices", proposed by the Japanese Research Society for Portal Hypertension. Also the two gastroenterologists separately reviewed the esophageal varices and decided the final grading in consensus.

4) To perform blind method, the radiologists should perform the measurement of HVPG without information of patients' diagnosis and clinical status.

Response: As HVPG measurement is invasive study, the measurements were done only in patients with known liver cirrhosis. Thus, it was impossible to perform measurement with totally blind method in this study.

5) There are several grammatical errors including the third sentence of the Core tip section. To improve the readability, the English writing of this manuscript should be polished.

Response: The language editing for the revised manuscript was done according to your recommendation.