PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Hepatic venous pressure gradient-guided laparoscopic splenectomy and pericardial devascularization versus endoscopic therapy for secondary prophylaxis for variceal rebleeding in portal hypertension (CHESS1803): Study protocol of a multicenter randomized controlled trial in China
AUTHORS	Shao, Ruoyang; Li, Zhiwei; Wang, Jitao; Qi, Ruizhao; Liu, Qingbo; Zhang, Weijie; Mao, Xiaorong; Song, Xiaojing; Li, Lei; Liu, Yanna; Zhao, Xin; Liu, Chuan; Li, Xun; Zuo, Changzeng; Wang, Weidong; Qi, Xiaolong

VERSION 1 – REVIEW

REVIEWER	Norberto Chavez-Tapia Medica Sur Clinic and Foundation (Mexico)
REVIEW RETURNED	09-May-2019

GENERAL COMMENTS	This very exciting protocol will provide very interesting information. However some issues should be considered before be published. 1. The title of this protocol is misleading and do not reflect the real intervention, in fact is quite unclear what the laparoscopic therapy is (the laparoscopic intervention is detailed until the hypothesis). I suggest included clearly the surgical intervention in the titled. 2. Is mandatory include a detailed report of adverse events, and length stay should be included. It is imperative include intra hospital mortality. 3. The inclusion criteria (c) is difficult to understand, as I read this trial it is aimed to assess two different approaches for secondary prevention of variceal bleeding. The criteria requires patients without previous endoscopy treatment, this is impossible or unethical. All previous bleeding requires endoscopic treatment. 4. The inclusion criteria (d) should be done before randomization (after hospitalization is unclear) 5. The exclusion criteria (c) specifically disturbed thrombocyte function shoul be defined properly. 6. The authors indicate the importance of HPVG at baseline (sample size estimation section) but HVPG is not included in the procedures section. 7. The abreviations should be clearly used and detailed.

REVIEWER	Said Ahmed Al-Busafi Sultan Qaboos University, Sultanate of Oman
REVIEW RETURNED	09-May-2019

GENERAL COMMENTS	Thanks for this interesting study protocol which is infinitely going to add new information to the management of acute variceal

	rebleeding. My questions and concerns to the authors are: 1. TIPS is less invasive comparing to the laparoscopic therapy, especially when talking about patient with high portal pressure and higher Child's score (B 7 to 9) 2. We know that Child's score B has higher peri-operative morbidity and mortality comparing to Child's A, how you can compare the outcomes of those to different population i.e. subgroup analysis 3. The laparoscopic therapy as you stated above is not yet used in many parts of the world especially west and its utility and when to to be used as a treatment modality for variceal bleeding is still not yet established. Therefore despite the positive results of this study, still it will be very difficult to apply (external validity) the results to other parts of the world apart from Asia.

REVIEWER	Tarek Sawas Mayo Clinic, USA
REVIEW RETURNED	13-May-2019

GENERAL COMMENTS	This is a well written protocol for a randomized controlled multicenter trail evaluating pressure gradient guided therapy for secondary prophylaxis of esophageal variceal bleed. The authors plan to include patients with liver cirrhosis and esophageal variceal beed with HVPG between 16-20 then randomize them to either laparsopy or endoscopy in combination with Propranolol. The primary outcome will be rebleeding. Secondary outcomes are survival, hepatocellular carcinoma, occurrence of venous thrombosis, quality of life and tolerability of treatment. The authors have a good plan for recruitment and randomization. They clearly explained the surgical procedure and outcome assessment. I have the following comments: 1. How soon after the the variceal bleed are you going to randomize patients? 2. How are the acute bleeding episode going to be managed? 3. Are you going to include patients who presented with recurrent esophageal bleeding 4. Could you please explain why you are interested with hepatocellular carcinoma as one of the outcome. What is the authors theory? Do you expect a decrease in HCC? Is 60 weeks followup enough for such outcome? 5. Could you please give more details about the cox regression model and the confounders which are going to be included in the model 6. The authors are planning to follow up patient for 60 weeks. what if a patient get a liver transplant, are they going to be censored at the time of transplant? 7. The authors did not provide plan about cross over. Is cross over allowed and when? 8. It is extremely concerning to perform surgery on patients with decompensated liver cirrhosis despite this being a minimally invasive surgery. Are there going to be any specific MELD cutoff where patients won't be included?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Comment 1
The title of this protocol is misleading and do not reflect the real intervention, in fact is quite unclear what the laparoscopic therapy is (the laparoscopic intervention is detailed until the hypothesis). I suggest included clearly the surgical intervention in the titled.

Response: Thank you for your suggestion. Using the expression “laparoscopic therapy” is mainly based on the intention to serve as the counterpart of “endoscopic therapy” which contains multiple different therapies. Yet, it is true that “laparoscopic therapy” is not enough to reflect the real therapy and may cause misleading. To address this drawback, the full name “laparoscopic splenectomy and pericardial devascularization” was used in the title and the first appearance in the abstract and main text, while “laparoscopic therapy” was used as its abbreviation afterwards. (line 1, 42 and 112)

Comment 2
Is mandatory include a detailed report of adverse events, and length stay should be included. It is imperative include intra hospital mortality.

Response: Thank you very much for your insightful advice. These points are definitely vital for measuring the acceptability and safety of interventions. Therefore, we added length stay and intra-hospital mortality in the outcomes section as outcome candidates. Length stay was now mentioned in the assessments section as part of data collection. Although adverse events have already been well mentioned in the original version, we further listed it as a secondary objective and outcome to emphasize its importance. Related description in the statistical analyses section was also modified. (line 55, 131, 137, 245 and 281)

Comment 3
The inclusion criteria (c) is difficult to understand, as I read this trial it is aimed to assess two different approaches for secondary prevention of variceal bleeding. The criteria requires patients without previous endoscopy treatment, this is impossible or unethical. All previous bleeding requires endoscopic treatment.

Response: Thank you very much for pointing out this severe clerical error. We actually meant that the participants should be without history of endoscopic therapy as secondary prevention. Patients are eligible for inclusion with any sense of managements upon acute bleeding except those who already received splenectomy. We revised this part for reflection of the real intention. (line 155)

Comments 4
The inclusion criteria (d) should be done before randomization (after hospitalization is unclear).

Response: Thank you for your constructive suggestion. As an item of inclusion criteria, it is obligatory to be performed before randomization. To clarify this, we mentioned it in the study design section and added it in the assessments section as a part of data collection. (line 143 and 256)

Comment 5
The exclusion criteria (c) specifically disturbed thrombocyte function should be defined properly.

Response: We appreciate your beneficial advice. Disturbed thrombocyte function intent to include all situations in which normal platelet function is disturbed and result in conglutination dysfunctions, covering congenital (Bernard-Soulier syndrome, Glanzmann thrombasthenia, storagepool disease, aspirin-like defects, platelet-type Von Willebrand disease, etc) and acquired (medication or other systemic diseases) causes. According to your concern, we listed these common situations in the corresponding section in the text. (line 166)

Comment 6
The authors indicate the importance of HPVG at baseline (sample size estimation section) but HVPG is not included in the procedures section.

Response: Thank you very much for pointing out this oversight. As mentioned in the response to comment 4, HVPG measurement was added in the study design section which indicates the overview of the study, and also the assessments section. (line 143 and 256) To further emphasize the importance of HVPG, we added a new section “HVPG measurement” describing the process of HVPG measurement. (line 191)

Comments 7
The abreviations should be clearly used and detailed.

Response: We really appreciate your beneficial comment and double-checked all abbreviations to be used in obedience to the guidance as suggested.

Reviewer 2

Comment 1
TIPS is less invasive comparing to the laparoscopic therapy, especially when talking about patient with high portal pressure and higher Child's score (B 7 to 9).

Response: Thank you very much for your insightful comment. Indeed, as an interventional radiological procedure, TIPS is a less invasive intervention compared to laparoscopic therapy. However, according to experiences in clinical practice, laparoscopic therapy is also an acceptable invasive surgery with low occurrence of severe complications for a large majority of patients stratified to be Child-Pugh class A and B with even high portal pressure.
TIPS is recommended for patients with HVPG higher than 20 mmHg. Nevertheless, there is not enough evidence to show that TIPS is superior for patients with HVPG between 16 and 20 mmHg. Moreover, as Lv et al reported recently, compared to medication, Child-Pugh class B patients accepting early TIPS were not benefitted in overall survival on a 1-year time scale[1].
Splenectomy and pericardial devascularization could increase liver perfusion and decrease portal pressure at the same time, while also ameliorate leukopenia and thrombocytopenia. Hence, this procedure is believed to benefit liver function and general condition of patients and consequently increase long-term survival. Yet, as you mentioned, it is combined with potentially higher intervention-related risk, together with increased risk of PVT and portal hypertensive gastropathy. On the other hand, although TIPS could significantly lower portal pressure, it also increases the occurrence of HE. Taking together, it is hard to assert which would be better for survival overall. As laparoscopic therapy is amongst the most commonly applied procedures in Asian-Pacific countries while have not yet been compared to the current standard of care, we chose to compare laparoscopic therapy to endoscopic therapy in this study, hoping for the most clinical applicational value. Nevertheless, we agree that it is also of great interest and importance to compare laparoscopic therapy to TIPS in future studies.

References:
1 Lv Y, Zuo L, Zhu X, et al. Identifying optimal candidates for early TIPS among patients with cirrhosis and acute variceal bleeding: A multicentre observational study. Gut 2018;:1–14. doi:10.1136/gutjnl-2018-317057

Comment 2
We know that Child's score B has higher peri-operative morbidity and mortality comparing to Child's A, how you can compare the outcomes of those to different population i.e. subgroup analysis.

Response: We appreciate your beneficial advice. We agree that performing subgroup analysis is vital for analysis. Therefore, we mentioned that subgroup analysis will be performed for Child-Pugh class A and class B patients respectively in the statistical analyses section. (line 344)

Comment 3
The laparoscopic therapy as you stated above is not yet used in many parts of the world especially west and its utility and when to to be used as a treatment modality for variceal bleeding is still not yet established. Therefore despite the positive results of this study, still it will be very difficult to apply (external validity) the results to other parts of the world apart from Asia.

Response: Thank you for your precious comment. It is absolutely true that there are wide gaps and differences lying among different regions of the world even when speaking of standard of care. Yet, the taking place of any change needs a beginning and much more effort. The aim of our study is to provide the initial high-level evidence for laparoscopic therapy. Although it is currently hard to be applied and even validated outside Asia, we believe this evidence will benefit clinical practice somewhat. Also, for Asian-Pacific regions where this therapy is widely applied, it is of great significance to know about its effectiveness and safety compared to other mainstream therapies.

Reviewer 3

Comment 1
How soon after the the variceal bleed are you going to randomize patients?

Response: Thank you for your precious comment. In this study, we concentrate on the effectiveness and safety of the two procedures as secondary prevention, requiring patients to be without active bleeding upon enrollment. Patients within the acute bleeding phase is not eligible for participating. Therefore, the interval between randomization and acute bleeding is not restricted or controlled. In order to avoid misleading, we added a new exclusion criterion to show clear that patients undergoing acute bleeding will not be included. (line 171)

Comment 2
How are the acute bleeding episode going to be managed?

Response: Thank you for your insightful comment. The acute bleeding episode will be managed with standard of care recommended by the Baveno VI guideline. Although as mentioned above, patients within the acute bleeding episode is not eligible for enrollment, this does work for patients that rebled during follow-up.

Comment 3
Are you going to include patients who presented with recurrent esophageal bleeding?

Response: Thank you for your beneficial comment. Taking into consideration that patients who already received multiple rounds of intervention usually have worse general condition and liver function that others, we are not going to include patients who presented with recurrent esophageal bleeding. We define secondary prevention as therapy for patients underwent acute bleeding without rebleeding yet.

Comment 4
Could you please explain why you are interested with hepatocellular carcinoma as one of the outcome. What is the authors theory? Do you expect a decrease in HCC? Is 60 weeks followup enough for such outcome?

Response: We appreciate your insightful concern very much. As demonstrated by Ripoll et al, patients with an HVPG higher than 10 mmHg suffer from an 6-fold-increased incidence of HCC[1], which was also suggested in the AASLD guideline[2]. Also, HCC is regarded as a secondary, especially long-term outcome in many studies[3,4]. Additionally, laparoscopic splenectomy and pericardial devascularization is believed to lower portal pressure while endoscopic therapy is not. Taking together, we expect that the incidence of HCC in the laparoscopic group to be decreased. Yet, we also agree that 60 weeks follow-up could be insufficient for the observance of significant difference, as we mentioned in the discussion section. In fact, follow-up will be continued for participants after the end of the study, somehow making up for this drawback.

1 Ripoll C, Groszmann RJ, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. J Hepatol 2009;50:923–8. doi:10.1016/j.jhep.2009.01.014
2 Garcia-tsao G, Abraldes JG, Berzigotti A, et al. Correction to: Portal Hypertensive Bleeding in Cirrhosis: Risk Stratification, Diagnosis, and Management: 2016 Practice Guidance by the American Association for the Study of Liver Diseases (Hepatology, (2017), 65, (310-335), 10.1002/hep.28906). Hepatology 2017;66:304. doi:10.1002/hep.29169

3 Piecha F, Mandorfer M, Peccerella T, et al. Pharmacological decrease of liver stiffness is pressure-related and predicts long-term clinical outcome. Am J Physiol Liver Physiol 2018;315:G484–94. doi:10.1152/ajpgi.00392.2017
4 Villanueva C, Albillos A, Genescà J, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2019;393:1597–608. doi:10.1016/S0140-6736(18)31875-0

Comment 5
Could you please give more details about the cox regression model and the confounders which are going to be included in the model?

Response: Thank you very much for this advice. The COX model will include age, sex, platelet, HVPG, AST, ALT, ALB, TBIL, MELD score and Child-Pugh score, as modified in the statistical analyses section. Also, MELD score is added in the assessment section as part of the data to be collected. (line 276 and 347)

Comment 6
The authors are planning to follow up patient for 60 weeks. what if a patient get a liver transplant, are they going to be censored at the time of transplant?

Response: We appreciate your beneficial suggestion very much. The patient should and will be censored when received liver transplantation. In the revised manuscript, this was clarified in the statistical analyses section. (line 344)

Comment 7
The authors did not provide plan about cross over. Is cross over allowed and when?

Response: Thank you for your insightful comment. Cross over will never be allowed in this study. Once rebleeding occurred, the patient will be managed according to the standard of care recommended by Baveno VI guideline instead of crossing over.

Comment 8
It is extremely concerning to perform surgery on patients with decompensated liver cirrhosis despite this being a minimally invasive surgery. Are there going to be any specific MELD cutoff where patients won't be included?

Response: Thank you very much for this incisive comment. According to experiences in clinical practice, laparoscopic splenectomy and pericardial devascularization is an acceptable invasive surgery with low occurrence of severe complications for a large majority of patients. In our study, eligible patients are further restricted to be Child-pugh Class A and B. These patients usually have fair general condition and liver function among all decompensated patients, and thus are rare to appear to be with a high MELD score. Hence, we did not set a MELD threshold for eligibility of enrollment. Nevertheless, we agree that MELD score may affect patients' outcome. As mentioned above, we included MELD score as a confounder in the COX regression model. (line 347)

VERSION 2 – REVIEW

REVIEWER	Norberto Chavez-Tapia Medica Sur Clinic & Foundation Mexico
REVIEW RETURNED	04-Nov-2019

GENERAL COMMENTS	The presence of 3 hypothesis is complicated, maybe some sub-analysis or sensitivity analysis could be included as exploratory aims. Please define clearly rebleeding as primary outcome.

REVIEWER	Said Al-Busafi Sultan Qaboos University Hospital, Sultanate of Oman
REVIEW RETURNED	30-Jul-2019

GENERAL COMMENTS	This is the second revision. It is much better written protocol, only few minor comments: - The title doesn't show if the interventions aimed for active rebleeding or secondary prophylaxis of rebleeding. So, the title should be like this (Hepatic venous pressure gradient-guided laparoscopic splenectomy and pericardial devascularization versus endoscopic therapy for secondary prophylaxis for variceal rebleeding in portal hypertension). - Still to me is not clear why they chose hepatocellular carcinoma as one of the secondary outcomes despite the short follow up duration of 60 weeks. I think this needs more explanation. - The informed consent should include details about the risks of the surgical intervention especially were her talking about secondary preventive measure not therapeutic. Also, what will be the management of those patient who do decompensate especially the subgroup at much higher risk i.e. Child's score of B? do they have a clear plan of doing liver transplant in an expedite manner in cases it is needed?

VERSION 2 – AUTHOR RESPONSE

Reviewer 1

Comment 1
The presence of 3 hypothesis is complicated, maybe some sub-analysis or sensitivity analysis could be included as exploratory aims.

Response: Thank you for your suggestion, we fully understood your concern. The hypotheses were arranged to match all our outcomes, including both effectiveness and safety. Nevertheless, we agree that the hypotheses, especially the third, looks complicated, and it is hard to assume which group will perform better in safety outcomes. Therefore, according to your suggestion, we deleted the original hypothesis 3 and split the original hypothesis 2 (dealing with overall survival and HCC) into two hypotheses dealing with one outcome only, hoping that this would make our hypotheses easily understood. (line 140 - 145) Please note that our outcomes were not and could not be modified and outcomes mentioned in the original hypothesis 3 will still be studied. As for sub-analysis, please kindly look up the statistical analyses section, line 361, which mentioned our plan about subgroup analysis.

Comment 2
Please define clearly rebleeding as primary outcome.

Response: Thank you very much for your suggestion. Please kindly check up the outcomes and assessments section, line 244 - 247, we have clearly defined variceal bleeding as primary outcome.

Reviewer 2

Comment 1
The title doesn't show if the interventions aimed for active rebleeding or secondary prophylaxis of rebleeding. So, the title should be like this (Hepatic venous pressure gradient-guided laparoscopic splenectomy and pericardial devascularization versus endoscopic therapy for secondary prophylaxis

for variceal rebleeding in portal hypertension).

Response: Thank you very much for your beneficial advice. The suggested title reflects much better the aim of our study, we have made modifications complying with your advice. (line 4)

Comment 2
Still to me is not clear why they chose hepatocellular carcinoma as one of the secondary outcomes despite the short follow up duration of 60 weeks. I think this needs more explanation.
Response: Thank you for your insightful comment, we completely understand your concern. The occurrence of hepatocellular carcinoma is highly related to increased portal pressure.[1] Due to the effect of decreasing portal pressure of laparoscopic therapy, we believe that this intervention will help reduce the incidence of hepatocellular carcinoma. Nevertheless, it is true that this outcome needs much longer follow-up. According to our plan, the participants will continue to be followed-up after the end of this study and longer-term results will be disseminated afterwards. To clarify this, we added some explanations to this issue in the discussion section. (line 413 - 419)

1 Ripoll C, Groszmann RJ, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. J Hepatol 2009;50:923–8. doi:10.1016/j.jhep.2009.01.014

Comment 3
The informed consent should include details about the risks of the surgical intervention especially were her talking about secondary preventive measure not therapeutic. Also, what will be the management of those patient who do decompensate especially the subgroup at much higher risk i.e. Child's score of B? do they have a clear plan of doing liver transplant in an expedite manner in cases it is needed?

Response: Thank you for your precious comments. In last round's submission, we uploaded the informed consent but mistakenly assigned it to be for editors only. We have changed the assignation of the consent form to make it available for reviewers. We have detailly described the possible risks throughout the study process and added in the safety section of the manuscript related contents. (line 330 - 336) For patients who reached the primary outcome, they will be managed according to the recommendation of Baveno VI guideline. (line 337 - 339) In cases it is needed, liver transplant will be done in an expedite manner. (line 339 - 340)