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Responses

Dear Reviewers and Editors:
We are very grateful to the reviewers and editors of the paper for their critical reading of the manuscript and many valuable recommendations for our further improvements. We have checked the manuscript and revised it according to the comments. More details are in the following.

Responses to reviewers:
Reviewer 2941224:
1. There are lots of grammatical errors throughout the text, especially symbol errors. For example, in the first sentence of introduction "…deaths each year, The mortality …" , should be replaced with. .
Responses: The article has been revised by a native English speaking expert. The edited paper has reached grade A in language evaluation for SCI journals.

2. "The mortality rate of HCC in China was 37.55 and 14.45 per 100,000" .. What is the exact rate? Should it be only one number?
Responses: We are sorry about that, this part was not clear in the original manuscript. We have revised the contents of this part, the number has been updated according to "Global cancer statistics, 2012" reported by Torre LA in CA Cancer J Clin. The sentence" with estimated 360,000 new cases, and 350,000 deaths each year. The mortality rate of HCC in China was 37.55 and 14.45 per 100,000" has been replaced by "with an estimated 391 250 new cases and 372 750 deaths in 2012. The mortality rate of HCC in China was 20.4 per 100 000 according to the 2015 annual report from the American Society of Clinical Oncology (ASCO)".

3. "HCC often stems from hepatitis B cirrhosis and combines with portal hypertension [2], such as the digestive tract hemorrhage and/or refractory ascites (or hydrothorax) [8, 9]; Patients with portal hypertension symptoms often have no opportunity to receive radical surgery or liver transplantation, even for interventional treatments, which adds importance to the treatment of portal hypertension symptoms that becomes urgent and core problem on that occasion" .. These sentences are quite redundant and contain lots of errors, for

example the symbol ";".
Responses: The sentence is divided and replaced by "HCC often stems from hepatitis B cirrhosis and combines with portal hypertension[2], leading to esophageal gastric-fundus variceal bleeding (EGVB) and/or refractory ascites (or hydrothorax)[8,9]. Patients with HCC and portal hypertension often have no opportunity to receive radical surgery or liver transplantation, or even some interventional treatments. It is important to manage portal hypertension urgently in patients with HCC[10] ". We suppose it would be better now.

4. The next sentence in the introduction is very long. It should be summarized. And the rest part of the introduction should be corrected as well.
Responses: The next sentence is divided and replaced by several sentences. As it is shown in the article: "Transjugular intrahepatic portosystemic shunt (TIPS) is an expandable metal stent inserted via the jugular vein that creates a shunt from the portal vein to the systemic circulation via an artificial communication through the liver. TIPS is widely used as a treatment of portal hypertension and its complications[11-14] (such as EGVB, refractory ascites, hepatic hydrothorax, hepatorenal syndrome, hepatopulmonary syndrome), and as a bridge to liver transplantation. Patients with portal hypertension have improvements in symptoms after TIPS, especially timely termination of acute EGVB and refractory ascites, which create opportunities for further treatment without affecting overall survival[15-17]". And the rest part of the introduction also has been revised by a native English speaking expert.

5. In the introduction, simple should be written as sample.
Responses: The article has been revised, and the sentence" The safety and efficacy of TIPS combining with other interventional treatments for patients with HCC and portal hypertension in the limited papers with small simple size turn out to be different, even paradoxical" has been replaced by "There are conflicting results about safety and efficacy of TIPS combined with other interventional treatments for patients with HCC and portal hypertension".

6. The authors included 209 of 261 patients for analysis. Why did the authors choose this group of population? What happened with the rest of patients?
Responses: We have not expressed clearly. The relevant parts in the article have been modified: "Two hundred and sixty-one patients with HCC and portal hypertension underwent TIPS combined with other interventional treatments (TACE/TAE, RFA, portal venous fistula embolization and splenic artery embolization) from January 1997 to January 2010 at Beijing Shijitan Hospital. We recruited 209 patients who had complete clinical data, and the rest of the patients who lacked such data were excluded". "Complete clinical data" are listed as "Clinical characteristics of the patients surviving ≥ 5 and <

5 years" in table 3.

7. In my opinion, the authors has combined the "result" of this study with the "method" part. The result (for example, characteristics of included patients, tumors, treatment received) should be placed in the "result" part of the manuscript.
Responses: We have rewritten "Clinical materials" part, which is divided into "Clinical materials" and "Methods" now. All of the characteristics of included patients were analyzed and compared in the table placed in the "results" part now. And the "Methods" part also has been rewritten, as it is shown in the article: "We evaluated the safety (procedure-related death and serious complications, such as abdominal bleeding, hepatic failure and distant metastasis), efficacy (change of portal vein pressure before and after TIPS, symptom relief, including ascites, hydrothorax, EGVB, and distributary channel restenosis) of the procedure, and the cumulative rates of survival. We also retrospectively analyzed and compared the clinical characteristics of patients living ≥ 5 and < 5 years, including sex, age, Child–Pugh score before TIPS, portal vein tumor thrombosis (PVTT), tumor lesion, lesion diameter, hepatic arterio-portal fistulas, cancer diagnosed before and after TIPS, stents used, treatments received (RFA, TACE/TAE, and RFA+TACE/TAE), and complications (recurrence of ascites/bleeding, hepatic encephalopathy, and channel function) that occurred during follow-up."

8. The result of patients characteristics contain a lot of grammatical and symbol errors.
Responses: The result of patients characteristics has been reviewed by a native English speaking expert, we suppose all the grammatical and symbol errors have been corrected.

9. What were the indications for TIPS placement? It should be clearly stated.
Responses: The indications and contraindications in these patients for TIPS placement have been clearly stated and listed in "TIPS" part already. Accumulated evidence has shown that indications of TIPS are being gradually expanded, the indications that the article involved are parts of them. "Indications: Acute or repeated variceal bleeding that failed conservative and endoscopic treatment; rebleeding after surgical shunting or laparosplenectomy; bleeding after preventive endoscopic/drug treatment; gastric or ectopic variceal bleeding; or refractory hepatic ascites/hydrothorax. Relative contraindications: Serious dysfunction of blood coagulation and bleeding tendency; hepatic encephalopathy; serious infections; portal vein thrombosis; cavernous transformation of portal vein; or tumor too large to avoid during TIPS. Patients with predicted survival ≤ 3 mo. Contraindications: Liver failure, severe cardiopulmonary dysfunction, multiple hepatic cysts, refractory biliopancreatic obstruction."

10. Why did the authors choose 5 years as a cutoff point for prognosis determination?
Responses: In consideration of "the 5 years survival rate" is widely used in the prognosis of patients with tumor. Moreover, the 5 years survival rate seems impressive and positive in the patients with hepatocellular carcinoma (HCC) and portal hypertension from what we have experienced. And the majority of these patients were followed up only for 5 years.

11. The first part of "therapeutic methods" is quite confusing. What is the main objective of this paragraph, to explain how to do the procedure or the describe how did the included patients receive the procedure? This should be rewritten.
Responses: This part was supposed to explain how did the included patients receive the procedure and the indications of TIPS for them. So we have rewritten this part already. The indications and contraindications for TIPS placement were clearly stated in this part. Moreover, in order to better display the process and the measure of portal vein pressure, some of the TIPS steps are also reserved. As you can see in the article: "The TIPS procedure was performed in the Interventional Radiology Suite under local anesthesia. The right jugular vein was punctured by RUPS-100 (Cook, Bloomington, United States) with a 10-F sheath. A 5-F multipurpose catheter was used to engage the hepatic vein (right usually) and the portal vein, perform portal vein angiography, and measure portal vein pressure before the shunting. A balloon catheter (6 or 8 mm in diameter) was used to expand the shunt along a guidewire, and the stents (7, 8 or 10 mm in diameter) were placed; and then portal vein angiography and measurement of portal vein pressure were conducted again."

12. What is the meaning of "1-11 times for each case."?
Responses: It was an inexact expression, Sorry about that, and it has been modified: "TACE or TAE was conducted before or after TIPS in 185 cases, from one to 11 times per patient". We suppose it would be better.

13. The figure legend should be placed at the lase part of the text. And hepatitis c should be written as C. There are some spelling and symbol errors in the figure legend as well.
Responses: The figure legend has been placed at the last part of the text ahead of the figures already. This part has been revised by a native English speaking expert, we suppose all the spelling and symbol errors have been corrected.

14. What is the meaning of "the end of death"?
Responses: It was an inexact expression and has been modified: "All cases were followed up until death or 5 years."

15. The "follow up" should be rewritten and proofread by persons with experience in academic English writing.
Responses: The "follow up" has been revised by a native English speaking expert, we suppose it would be appropriate now.

16. What was the main objective of this study? It should be firstly described in the result part.
Responses: The main objective of this study was to evaluate efficacy (change of portal vein pressure pre and after TIPS, symptoms relieving), the safety of TIPS combining with other interventional treatments and also the possible factors that may affect the 5-year survival of the patients. So we have made an adjustment for the representation of "results". The previous part 3 together with the previous part 2 of the results have been putted together and presented firstly. As you can see:

"The pre-TIPS portosystemic pressure was 29.0 ± 4.1 mmHg, which decreased to 18.1 ± 2.9 mmHg ($t = 69.32$, $P < 0.05$) after TIPS. The portal hypertension symptoms were relieved and improved; the rates of resistant ascites, hydrothorax, EGVB, hepatic encephalopathy and distributary channel restenosis during follow-up were relatively impressive. Details including the interventional re-treatments for distributary channels and interventional treatments for tumor lesions are all presented in Table 1.

Clinical characteristics of patients living $\geqslant$ 5 and < 5 years were analyzed and compared: patients' sex mean age, lesion number, recurrence (ascites/bleeding), and TIPS channel function did not differ significantly between the two groups ($P > 0.05$). Moreover, Child–Pugh score, with or without PVTT, lesion diameter, hepatic arterio-portal fistulas, cancer diagnosed before or after TIPS, stent type, hepatic encephalopathy, and interventional treatment differed significantly between the two groups ($P < 0.05$) (Table 3).

No procedure-related deaths or serious complications (e.g. abdominal bleeding, hepatic failure and distant metastasis) occurred. The main causes of death during follow-up were: 36 cases of gastrointestinal rebleeding, which caused hemorrhagic shock, acute liver failure and hepatic encephalopathy, and some of them died out of hospital. Thirty-one cases died of liver failure or multiple organ failure; 29 of abdominal or lung infection; and 19 of tumor progression, which lead to respiratory and circulatory failure. Other causes of death were hepatorenal syndrome and cardiovascular and cerebrovascular diseases."

17. The pre-TIPS PSG was very low (3.87). I am surprised that this low pressure gradient could cause the symptoms of portal hypertension.
Responses: The portosystemic pressure is relatively low in the patients with acute esophageal varices bleeding and ectopic varices, expecially the patients

with large amount of shunt or massive bleeding. On the contrary, the portosystemic pressure is relatively high in the patients with refractory ascites. Moreover, we recruited 209 patients, EGVB was seen in 182 cases, refractory ascites (and/or pleural effusion) in 39, and refractory ascites (and/or pleural effusion) combined with EGVB in 12. 29.03mmHg (3.87 kPa) is the mean pressure of these patients, in spite of relatively lower compared with common patients with portal hypertension.

18. What was the unit of pressure gradient that the authors measured? Normally, we use mmHg.
Responses: The unit of pressure gradient is supposed to be "mmHg" normally, and "kPa" has been replaced by "mmHg" already. As it is shown in the article "The pre-TIPS portosystemic pressure was 29.0 ± 4.1 mmHg, which decreased to 18.1 ± 2.9 mmHg after TIPS."

19. The part 3 of the result should be rewritten. The authors should points out the important point from the analysis in the text. And, in my opinion, it is not necessary to report the survival and restenosis every year from 1-5. Again, there are symbol errors.
Responses: We have made an adjustment for the representation of "results". The previous part 3 together with the previous part 2 of the results have been putted together. The important points from the analysis are expressed: "The pre-TIPS portosystemic pressure was 29.0 ± 4.1 mmHg, which decreased to 18.1 ± 2.9 mmHg ($t = 69.32$, $P < 0.05$) after TIPS. The portal hypertension symptoms were relieved and improved; the rates of resistant ascites, hydrothorax, EGVB, hepatic encephalopathy and distributary channel restenosis during follow-up were relatively impressive. Details including the interventional re-treatments for distributary channels and interventional treatments for tumor lesions are all presented in Table 1". As you can see more details in responses to comment "16".
Moreover, It is not necessary to report the survival rate every year from 1-5, which has been removed from the Table 1.
As to the restenosis rate, we believe that TIPS especially using bare stents is easy to develop shunt stenosis or occlusion, and this can increase the symptoms' recurrence rate, which may not only seriously affect the patients quality of life, the patients' survival, but also the interventional re-treatments. So we consider that it would be better to reserve " the restenosis rate every year from 1-5" , in order to emphasize the importance of it, as we are discussing with you.

20. In the last part of the result, the authors should state the important and main finding of their study in the proper and universal pattern. Did the authors perform regression analysis of their data? The detailes causes of death should be explained.

Responses: The important and main finding of the study were already stated in the last part of the result now. As it is shown in the article: "Thus, the portal hypertension symptoms were ameliorated after TIPS and other interventional treatments with no procedure-related deaths and serious complications. Moreover, Child–Pugh score, PVTT, lesion diameter, hepatic arterio-portal fistulas, HCC diagnosed before or after TIPS, stent type, hepatic encephalopathy, type of other interventional treatments were related to 5-year survival after comparing the characteristics of patients living ≥ 5 and < 5 years". Unfortunately, the disadvantage of this article is that we did not perform regression analysis of the data, which is difficult for us to do so now, and we hope to improve in the future research.
The detailes causes of death also have been explained in the "results" part: The main causes of death during follow-up were: 36 cases of gastrointestinal rebleeding, which caused hemorrhagic shock, acute liver failure and hepatic encephalopathy, and some of them died out of hospital. Thirty-one cases died of liver failure or multiple organ failure; 29 of abdominal or lung infection; and 19 of tumor progression, which lead to respiratory and circulatory failure. Other causes of death were hepatorenal syndrome and cardiovascular and cerebrovascular diseases.

21. Unfortunately, I don't understand the main idea, including the result, of this manuscript very well. Therefore, I couldn't make a comment on the discussion part right already. I would suggest the authors to revise the manuscript first and send it back for second revision. However, a lots of grammatical and symbol errors are n
Responses: The comments showed in the system seem not complete, which is end up with "n".

Reviewer 2155130:

1) The "result" and "method" part should be clarify. The result (for example, characteristics of included patients, tumors, treatment received) should be placed in the "result" part of the manuscript.

Responses: We have rewritten "Clinical materials" part, which is divided into "Clinical materials" and "Methods" now. All of the characteristics of included patients were analyzed and compared in the table placed in the "results" part now. And the "Methods" part also has been rewritten, as it is shown in the article: "We evaluated the safety (procedure-related death and serious complications, such as abdominal bleeding, hepatic failure and distant metastasis), efficacy (change of portal vein pressure before and after TIPS, symptom relief, including ascites, hydrothorax, EGVB, and distributary channel restenosis) of the procedure, and the cumulative rates of survival. We also retrospectively analyzed and compared the clinical characteristics of patients living ≥ 5 and < 5 years, including sex, age, Child－Pugh score

before TIPS, portal vein tumor thrombosis (PVTT), tumor lesion, lesion diameter, hepatic arterio-portal fistulas, cancer diagnosed before and after TIPS, stents used, treatments received (RFA, TACE/TAE, and RFA+TACE/TAE), and complications (recurrence of ascites/bleeding, hepatic encephalopathy, and channel function) that occurred during follow-up."

2) The result of patients characteristics should be checked again.
Responses: We have checked the data of patients characteristics again carefully.

3) What were the indications for TIPS placement? It should be clearly stated.
Responses: The indications, relative contraindications and contraindications of TIPS placement in these patients have been clearly stated in "TIPS" part already: "Indications: Acute or repeated variceal bleeding that failed conservative and endoscopic treatment; rebleeding after surgical shunting or laparosplenectomy; bleeding after preventive endoscopic/drug treatment; gastric or ectopic variceal bleeding; or refractory hepatic ascites/hydrothorax. Relative contraindications: Serious dysfunction of blood coagulation and bleeding tendency; hepatic encephalopathy; serious infections; portal vein thrombosis; cavernous transformation of portal vein; or tumor too large to avoid during TIPS. Patients with predicted survival $\leqslant$ 3 mo. Contraindications: Liver failure, severe cardiopulmonary dysfunction, multiple hepatic cysts, refractory biliopancreatic obstruction."

Reviewer 807135:

1. Some language polishing need to be corrected. A native English speaker is required to proof the manuscript.

Responses: The article has been revised by a native English speaking expert. The edited paper has reached grade A in language evaluation for SCI journals.

2. The sentence in the introduction is very long. It should be summarized.
Responses: The long sentence is summarized, divided and replaced by several sentences. As it is shown in the article: "HCC often stems from hepatitis B cirrhosis and combines with portal hypertension[2], leading to esophageal gastric-fundus variceal bleeding (EGVB) and/or refractory ascites (or hydrothorax)[8,9]. Patients with HCC and portal hypertension often have no opportunity to receive radical surgery or liver transplantation, or even some interventional treatments. It is important to manage portal hypertension urgently in patients with HCC. Transjugular intrahepatic portosystemic shunt (TIPS) is an expandable metal stent inserted via the jugular vein that creates a shunt from the portal vein to the systemic circulation via an artificial communication through the liver. TIPS is widely used as a treatment of portal

hypertension and its complications[11-14] (such as EGVB, refractory ascites, hepatic hydrothorax, hepatorenal syndrome, hepatopulmonary syndrome), and as a bridge to liver transplantation. Patients with portal hypertension have improvements in symptoms after TIPS, especially timely termination of acute EGVB and refractory ascites, which create opportunities for further treatment without affecting overall survival".

3. The "follow up" should be re-arranged.

Responses: The "follow up" has been revised by a native English speaking expert, we suppose it would be better now. As to the "results" of the follow up, the "results" and "method" part have been clarified. All of the characteristics of included patients were analyzed and compared in the table placed in the "results" part now.

4. References should be update.

Responses: Serval references have been updated. Such as the number of HCC deaths in china has been updated according to "Global cancer statistics, 2012" reported by Torre LA in CA Cancer J Clin. The sentence "with estimated 360,000 new cases, and 350,000 deaths each year" has been replaced by "with an estimated 391 250 new cases and 372 750 deaths in 2012". We also update the mortality rate of HCC in China: "The mortality rate of HCC in China was 20.4 per 100 000 according to the 2015 annual report from the American Society of Clinical Oncology (ASCO)". So as the references: 13, 15-17, 33.

Responses to editors:

1. The article has been revised by a native English speaking expert from Jing-Yun Ma Editorial Office, one of the professional English language editing companies mentioned in 'The Revision Policies of BPG for Article. The edited paper has reached grade A in language evaluation for SCI journals.
2. The "Institutional review board statement, Informed consent statement, Conflict-of-interest statement, Data sharing statement" are stated carefully in the article.
3. The figures have been edited.

Finally, we look forward to hearing from you regarding our submission. We would be glad to respond to any further questions and comments that you may have.

Thank you for your time.

Fuquan-Liu