October 25, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4911-review.doc).

Title: An Accurate Predictor of Liver Failure and Death after Hepatectomy: A Single Institution's Experience with 478 Consecutive Cases

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The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer.

First, we thank the reviewer for his/her positive and constructive comments and suggestions. We have answered all the questions and comments below. We hope that our responses are adequately explanatory.

1) I do not think that their aim to define PLF is fulfilled their work attempts to predict morbidity and mortality but does not define this entity.
Answer: Thank you for your careful review and valuable suggestions. We have paid attention to this issue and have rewritten the text to make the definition more precise in the revised manuscript. In the present study, we sought to recommend a precise definition of PLF and to then predict liver

failure-related morbidity. Due to the lack of a standard definition of PLF, whether a patient suffers liver failure-related death after liver resection is generally determined by experience in the clinic. Thus, establishing a standard definition of PLF that can precisely predict liver failure-related death in a timely fashion is particularly important. Because the hepatic damage score (HDs) was highly correlated with liver failure-related death and was validated in the present study, we believe that the HDs provides a good definition of PLF. Furthermore, the HDs can define the degree of metabolic functional impairment after resection as mild (HDs = 0), reversible hepatic "dysfunction" (HDs = 1) or fatal hepatic failure (HDs = 2), which is more important for its clinical use.

The HDs can reflect the function of the remnant liver after liver resection, similar to the ability of the Child-Turcotte-Pugh (CTP) to evaluate the hepatic function of patients with end-stage liver disease. HDss of 0, 1 and 2 were similar to CTP grades A, B and C. However, the HDs differs from the CTP grades in two ways. First, the CTP grade is typically used to evaluate the hepatic function of patients with end-stage liver disease and is rarely used in the early postoperative period due to the large number of subjective factors included in it, such as ascites and hepatic encephalopathy, which may be affected by surgery. Second, the CTP grade cannot precisely reflect changes in hepatic function change; for example, patients can exhibit an increase in total bilirubin without a change in the CTP grade. The HDs was derived from TBIL-r1 and INR-r1, which can precisely reflect changes in liver function, and may predict the endpoints in a timely fashion.

Although the HDs can precisely predict liver failure-related death, it can only be used postoperatively. So we investigated predictors of the HDs next step.

2) I also think that they do not show a valid way to determine the risk preoperatively.

Answer: Because the HDs was shown to be a reliable and standardized definition of PLF, we investigated predictors of the HDs. If we can preoperatively predict the patient HDs, the operation may be safer. In the present study, we found two independent risk factors to predict the HDs. Using these two parameters, we determined a regression formula for patients with an HDs of 2.

The regression formula can help to determine the risk preoperatively. First, once a patient's ICG-R15 value is determined, we can use the formula to calculate the number of segments that can be resected. Then, we can analyze the CT images of the patient and assess the number of segments that need to be resected during the hepatectomy. As indicated by the results presented in the revised manuscript, patients who require the resection of a greater number of segments than the value calculated by the equation are at higher risk following hepatectomy (with higher liver failure-related mortality and morbidity due to major complications). Therefore, in patients who require the resection of a greater number of segments than the value calculated by the equation, hepatectomy is riskier, and additional adjuvant therapies may be necessary pre- or postoperatively, including portal vein embolization before hepatectomy, an artificial liver support system after resection or even opting for therapies instead of hepatectomy.

3) I think they have done a good job in presenting the evidence that their measures predict mortality and perhaps morbidity when used in the early post-period but I am not convinced that their resistance measures are superior to simple INR and TBil.

Answer: We thank you for this valuable comment. We agree that the coined terms of TBIL-resistance and INR-resistance may not be easy to understand for all readers. Accordingly, we have accepted your suggestion and used the terms TBIL-r1 and INR-r1 instead of TBIL-resistance and INR-resistance, respectively, in the revised manuscript.

We originally wanted to use just the TBIL and INR parameters for analysis; however, their predictive powers were not as strong as those of the ratios of these two parameters. For example, on POD 3, there were no differences in TBIL or INR between the two groups; however, significant differences in the TBIL-r1 and INR-r1 were noted. On POD 5, the areas under the ROC curves (AUCs) were 0.810 and 0.708 when using TBIL and INR, respectively; however, the AUCs reached 0.917 and 0.716 for TBIL-r1 and INR-r1, respectively. Because the early diagnosis of postoperative liver failure is vital for optimal management, we chose to analyze TBIL-r1 and INR-r1 in the revised manuscript all the same. A comparison of these two types of parameters regarding their predictive power was added to the revised manuscript.

We speculate that the reasons for the stronger predictive powers of TBIL-r1 and INR-r1 compared to those of TBIL and INR are as follows. (1) The majority of patients slowly developed postoperative liver failure, and hyperbilirubinemia, coagulopathy, hypoalbuminemia and different grades of hepatic encephalopathy could only be detected after POD 7 or even after POD 30. Thus, although the levels of TBIL and INR were low in the first several days postoperative, liver failure could ultimately still occur. If we simply used TBIL and INR as predictive parameters, the patients could not be diagnosed as having postoperative liver failure because the TBIL and INR values were not sufficiently high. However, TBIL-r1 and INR-r1 are ratios, which can more precisely detect variations in TBIL and INR and can more accurately predict postoperative liver failure than TBIL and INR. (2) Liver resection is a type of major surgery, and the burden on the patients is immense. Therefore, in patients who undergo complex or extended liver resection, the liver may have large cut faces with a great amount of hepatocyte necrosis during the operation. Although the liver function may recover, which is reflected in the stability and slight decrease in the TBIL and INR levels, respectively, in the days following the operation, the TBIL and INR levels may also be high in the

first several days postoperative. If we use TBIL and INR to predict PLF, the result may be biased in these patients.

In the clinic, the TBIL and INR values of the majority patients vary significantly from before liver resection to POD 1. In most situations, TBIL and INR increase significantly on POD 1 and POD 3 to their preoperative values. If TBIL-r1 and INR-r1 are calculated based on the preoperative values, the data may be biased by the operative procedure. Therefore, we examined the POD 1 values for TBIL-resistance and INR-resistance (now revised to TBIL-r1 and INR-r1, respectively) as possible postoperative predictors of PLF.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,
Bo Li and ZhengGui Du

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