Peer Review File

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Reviewer A

This paper describes the hepatectomy-related complications and prediction model. Although the paper is interesting, it includes several problems as follows.

1. When hepatectomy-related complications are discussed, indication criteria of hepatectomy must be clearly described. I cannot find any description on indication.

Reply: Thanks for the reviewer's comment and suggestion. Hepatectomy is a routinely performed clinical procedure in hepatobiliary surgery, as we have made clear in the first sentence of the text(Hepatectomy is a curative treatment of benign and malignant primary hepatobiliary tumors, metastatic liver tumors, intrahepatic bile duct stones, and other hepatobiliary system diseases.).In addition, in the case inclusion criteria for this study, we specified that the included cases undergoing hepatectomy needed to meet the condition that the extent of resection was more than 3 liver segments.
Changes in the text: In order to give the reader a clearer understanding of the case population and study conditions, we have adjusted the content of the article to include the names and subgroups of diseases of the hepatobiliary system in the "Participants" section.

2, How did the authors evaluate liver function?

Reply: Thanks for the reviewer's comment and suggestion. In the present study, all enrolled cases were evaluated on the basis of serological laboratory tests and in combination with Child-Pugh scores on the patients' liver function. Cases with Child-Pugh class A and B liver function assessment were included in the study. Patients with Child-Pugh grade C liver function assessment, which is widely accepted in clinical practice, were excluded from the study due to their severely poor liver function and their inability to tolerate hepatectomy.

3. When bile leakage is discussed, the cases with bile duct resection should not be included.

Reply: Thanks for the reviewer's comment and suggestion. The bile duct system consists of the intrahepatic bile duct system and the extrahepatic bile duct system. In order to standardize the uniform definition and severity grading of bile leakage after hepato-pancreatic surgery, the International Study Group of Liver Surgery (ISGLS) reached a consensus in 2011 on the definition of bile leakage after hepatopancreatic surgery based on the changes of bilirubin concentration in serum and drainage fluid of postoperative patients. In this consensus, the ISGLS did not exclude the case population with combined extrahepatic bile duct resection. Therefore, in this study therefore we also did not exclude cases of combined extrahepatic bile duct system resection.

Reviewer B

The paper titled "The cohort study of hepatectomy-related complications and prediction model for postoperative liver failure after major liver resection in 1441 patients without obstructive jaundice" is interesting, which showed a high perioperative safety and a low risk of serious complications in patients who underwent major liver resection at a large hepatobiliary surgery center. Routine preoperative clinical information can be used to develop a postoperative liver failure risk prediction model for rational planning of surgery. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) This study is the result of a single-center large cohort analysis, and an external cohort needs to be further tested for its effectiveness and accuracy.

Reply: Thanks for the reviewer's comment and suggestion. The results based on the single-center cohort study data are a weakness of this study, which we have pointed out in the "LIMITATION" section of the article. We look forward to the following multicenter studies or the findings of other centers to validate our single-center results.

2) The identifications of the figures in the manuscript are inconsistent with those in the figure legends. Uniform identification is recommended.

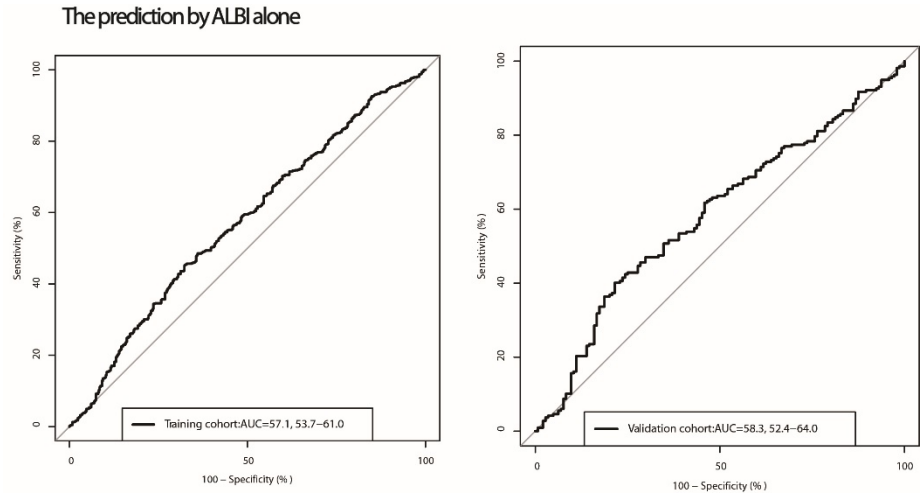
Reply: Thanks for the reviewer's comment and suggestion. We have proofread and supplemented this section.

3) There are many other unclear risk factors that affect the results of the model. How to treat and solve this problem?

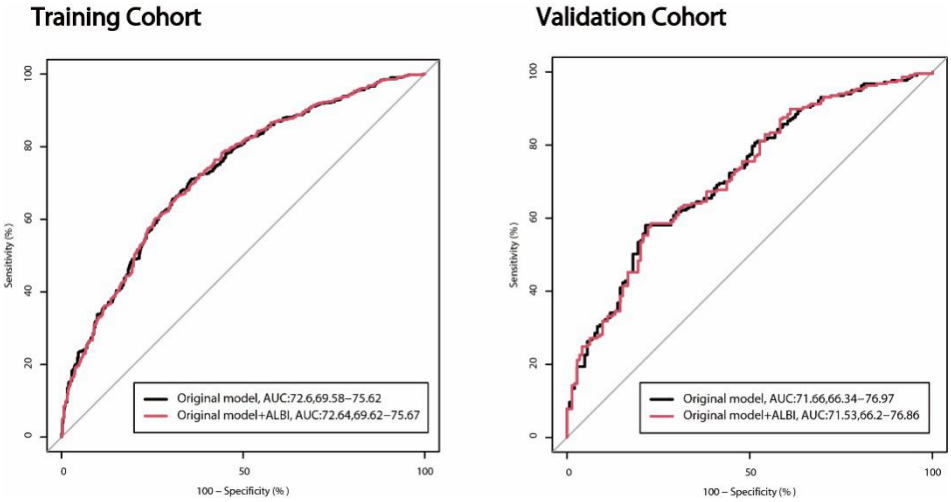
Reply: Thanks for the reviewer's comment and suggestion. Indeed, as pointed out by the reviewers, there may be many potential influences on the development of postoperative liver failure in patients undergoing hepatectomy that were not included in this study. However, the main purpose of this study was to use routine preoperative clinical information to establish a postoperative liver failure prediction model, so we conducted statistical analysis and model construction based on the preoperative and intraoperative risk factors that may be associated with liver failure based on current clinical consensus. We expect that more basic and clinical studies on liver function will be conducted in the future, which will give us a clearer understanding of the exact mechanisms and risk factors of liver failure and help us to further improve the accuracy of the liver failure prediction model.

4) It is recommended to increase the Child-Pugh score and ALBI score of liver function to predict the receiver operating characteristic curve analysis of liver failure after hepatectomy.

Reply: Thanks for the reviewer's comment and suggestion. In the "Inclusion criteria", we included the patients with Child-Pugh score of A or B. Additionally, the most of patients in our study were Child-Pugh score of A (99.17%), and there was no significant difference of Child-Pugh score between Non-PHLF group and ISGLS-PHLF group (P=0.9385). Therefore, we considered that Child-Pugh score would no increase the prediction effect of model.
For the ALBI score, we conducted the ROC analysis with ALBI score only, and the AUC was only 57.1% for training cohort (58.3% for validation cohort).



Furthermore, we added the ALBI score in our model. The AUC of original model plus ALBI score were similar with the AUC of original model in training and validation cohort. The original model was established with the original routine preoperative clinical information. However, the ALBI score were calculated with TBIL and ALB, and this score did not improve the prediction effect of our model. Therefore, we would not included this score in our model.



5) What is the follow-up and survival of the patients in this study?

Reply: Thanks for the reviewer's comment and suggestion. This study is a cohort study of perioperative complications of major liver resection and is not a correlative study of clinical outcomes for long-term prognosis; therefore, the article focuses on the risk factors associated with hepatectomy. In addition, the cases included in this study included malignant tumors and benign occupying diseases of the liver, and studies related to postoperative survival of patients with different diseases could not be compared according to uniform research standards.

Therefore, for these reasons the long-term survival of all cases in the cohort has not been statistically and analytically analyzed in our study at this time.

6) Is it compared with patients with obstructive jaundice? The introduction and comparison of patients with obstructive jaundice should be added, which may be more meaningful

Reply: Thanks for the reviewer's comment and suggestion. The ISGLS definition of postoperative liver failure is based on the status of recovery of liver function in patients on postoperative days 4 and 5 as a criterion for assessing whether liver failure has occurred. Relevant laboratory parameters include serum total bilirubin and coagulation parameters INF to reflect the recovery of hepatocyte function after surgery. A significant preoperative increase in serum bilirubin due to biliary obstruction does not necessarily mean that the patient's hepatocyte function is severely impaired and irreversible. Therefore, the ISGLS definition of postoperative liver failure clearly states that other obvious causes for the observed biochemical and clinical alterations such as biliary obstruction should be ruled out. Consistent with the inability to use the Child-Pugh score for preoperative assessment of liver function in patients with obstructive jaundice, the use of the ISGLS criteria for postoperative liver failure is difficult to apply accurately to patients with obstructive jaundice. Therefore, in order to accurately focus on the risk factors associated with the development of postoperative liver failure, cases of obstructive jaundice were excluded from our study and are described in the article title and study exclusion criteria. We plan to follow up with a study on cases with obstructive jaundice.

7) What are the causes, treatment measures and prognosis of the patients' complications in this study? What is the significance for predicting postoperative liver failure?

Reply: Thanks for the reviewer's comment and suggestion. We performed a multifactorial analysis of risk factors associated with perioperative complications after hepatectomy in the total cohort, identifying preoperative risk factors for each type of complication (see Table s3. Multivariable analyses of post-hepatectomy outcomes in total cohort). Complications such as postoperative hemorrhage and bile leaks were also analyzed in relation to liver failure (see Table s2. Intra-operative procedure and post-hepatectomy outcomes in total cohort for specific information). Therapeutic measures for various complications and patients' prognosis were not the main objective of this study, and therefore they are not discussed as the main topic in this article. In addition, the main purpose of this

study was to use routine preoperative clinical information to develop a predictive model of postoperative liver failure, so the construction of a predictive model to include other postoperative complications was not performed