

Dear Editor,

Thank you very much for your decision letter and advice pertaining to our manuscript entitled, “Drainage fluid and serum amylase levels accurately predict development of postoperative pancreatic fistula” (Manuscript 33466). We also thank the reviewers for the constructive and positive comments and suggestions. Accordingly, we have revised the manuscript. All amendments are highlighted in red in the revised manuscript. In addition, point-by-point responses to the comments are listed below this letter.

This revised manuscript has been edited and proofread by a professional medical editing company.

We hope that the revision is acceptable for publication in your journal.

Look forward to hear from you soon.

With best wishes,

Yours sincerely,

Guang-yi Wang

First of all, we would like to express our sincere gratitude to the reviewers for their constructive and positive comments.

## Replies to Reviewer 1

### COMMENTS TO AUTHORS

Dear Editor, Thank you for the opportunity to review this well conducted scientific research! The authors correlate the postoperative clinical factors with POPF rate, including prospectively 83 patients with pancreaticoduodenectomy. I suggest some minor modifications:

? Check the spelling and the grammar of the manuscript.

? The rate of POPF (33.7%) is higher from that of the literature. Please discuss that!

? Cut – off value (44.2 u/l) for serum amylase level is normal. What is the relevance of this conclusion? Please specific the accuracy, PPV, NPV, specificity and sensibility of a cut off value above maximum, normal value.

? Details of clinical management –”fixed to the pancreatic parenchyma before surgery?” How that? Please detail!

Therefore, I recommend it for publication, after minor revision. Best wishes, Ionut

#### 1、 Response:

1) According to the references, complication rates of pancreatic fistula ranged from 2 to 25%. We obtained the data strictly according to the inclusion and exclusion criteria. We only enrolled 83 patients in this study; the small sample size may have contributed to the higher fistula rate. Secondly, all the operations were performed by two surgeons with experience of more than 100 surgical cases.

2) As rightly pointed out, we found serum amylase level of 44.2 U/L on POD4 to be an effective maker. This value is within the normal reference range for serum amylase; thus we believe that serum amylase on POD4 higher than 100 U/L is probably more appropriate to have an optimal predictive effect. Therefore, serum amylase levels still higher than 100 U/L indicated a high possibility of pancreatic fistula.

We have included the data on PPV, NPV, specificity, and sensitivity of serum amylase on POD1 and POD4, and for amylase level in ascitic fluid on POD1. The upper limit of normal serum amylase was at 100 U/L, whereas it was 300 U/L for amylase levels in the ascitic fluid. Serum amylase on POD1 with a discriminatory threshold of 100 U/L predicted POPF with an 82.1% sensitivity, 61.8% specificity, 40.4% PPV, and 19.2% NPV. Serum amylase on POD4 with a discriminatory threshold of 100 U/L predicted POPF with a 42.9% sensitivity, 55% specificity, 75% PPV, and 76.1% NPV. The amylase level in abdominal drainage fluid on POD1 with a discriminatory threshold of 300 U/L predicted POPF with 100% sensitivity, 80% specificity, 38.8% PPV, and 100% NPV. We further found that amylase activity in drain fluids on POD1 and serum amylase activity on POD4 could accurately predict POPF

3) It should be “during the surgery” here. The surgical techniques and perioperative management were as follows. All patients underwent PD using Child procedure with an intraoperatively placed pancreatic drainage tube. The anastomotic procedure involved end-to-end

invaginating pancreaticojejunostomy with the insertion of a drainage tube into the major pancreatic duct. 43 patients underwent PD using Child's procedure with an external pancreatic drainage tube (size: 6, 7 or 8) fixed to the pancreatic parenchyma during the pancreaticojejunostomy, and then the tube was routed out of the body via the distal bowel. And 40 patients underwent PD using Child's procedure with an intraoperatively placed external pancreatic drainage tube (size: 6, 7 or 8) fixed to the pancreatic parenchyma, which was left in the bowel. We used a 5-0 non-absorbable suture to close the posterior wall of the pancreaticojejunostomy anastomotic opening; we used a 4-0 polyethylene continuous suture to lock-stitch the anterior and posterior walls and to embed the anterior urothelium. The drainage tubes were placed above and below the pancreaticojejunostomy anastomotic opening and below the biliary anastomotic opening. All patients were administered sulbactam/cefoperazone (3.0 g/Q12 h) as preoperative prophylaxis and for the first 6 days after PD to prevent postoperative infection. Prophylactic intravenous octreotide was administered at a dose of 0.6 mg/24 h for the first 3 days after surgery to decrease the rate of pancreatic secretion.

## **Replies to Reviewer 2**

### **COMMENTS TO AUTHORS**

In this manuscript, the authors analyzed the potential correlation between biomarkers and postoperative complications such a pancreatic fistula. Please, could you discuss what actions can be derived from these results, to optimize the treatment of POPF?

Response: Although recent advances in surgical techniques have reduced the rate of POPF, it still continues to be relatively high. There is a need for surgeons to identify patients who are at high risk of POPF soon after the surgery.

Our results may help us identify such patients and allow interventions to help prevent its occurrence, for example, by prolonging the fasting time and applying enzyme inhibition. In addition, it may help the doctor to predict the occurrence of pancreatic fistula, and allow for timely risk-communication to the patient.