ANSWERING REVIEWERS

April 24, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format

Title: Analysis of risk factors for postoperative pancreatic fistula following pancreaticoduodenectomy in the Chinese PLA General Hospital

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Name of Journal: *World Journal of Gastroenterology*

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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

To 00057645-reviewer as follows:

(1) The Chinese PLA General Hospital is the largest comprehensive hospital in the army, integrating clinical treatment, health care, education and research functions. The PLAGH has 125 clinical, medical and technological departments, 4000 patient beds, and annual volumes of more than 3.8 million outpatient visits, over 110000 admissions and more than 65000 operations. The volume of pancreaticoduodenectomy is about 200-400 per year and near the top in China. Data of the center is more representative.

The diagnosis of postoperative pancreatic fistula and clinical relevant postoperative pancreatic fistula is judged very strictly according to the ISGPF definition. Amylase level of drainage fluid was evaluated on postoperative period routinely in every patient who underwent PD until discharged from hospital. The essential component of an anastomotic leak was the high amylase content (> 3 times the upper normal serum value), of the drain fluid (of any measurable volume), at any time on or after the 3rd postoperative day. The issue was however further compounded by the concept of "clinical relevance", a phrase often employed to distinguish asymptomatic biochemical POPF from those that are associated with clinical illness, therapeutic intervention, or death. When associated with abdominal pain, fever, and/or leukocytosis, antibiotics are usually required, finally, the POPF shifts into grade B. If an invasive procedure is needed, the POPF shifts into grade C.

The overall percentage of fistulas of 64.3% is high compared to what is reported in the literature, as well as the percentage of clinically relevant fistulas (CR-POPF 32.7%). It is an astonishing result, but it is the reality. Different surgeons who performed the PD maybe attribute the high percentage of fistulas.

(2) For patients with periampullary tumor, the RCTs and meta-analyses showed no benefit of preoperative biliary drainage. Instead, there were some concerns about the drainage-related complications and the increase in positive intraoperative bile culture rate and the associated infective complication rate postoperatively. In the Chinese PLA General Hospital, preoperative biliary drainage has not been developed routinely before pancreaticoduodenectomy for patients with periampullary tumor. Furthermore, preoperative biliary drainage related to morbidity or mortality rate but showed no relation to postoperative pancreatic fistula. Accordingly, we did not choose preoperative biliary

drainage as a risk factor.

(3) The univariate analysis was performed on table 2 consisted of patients with POPF of any grade versus no POPF in the first column and patients with CR-POPF versus no POPF-grade A POPF in the second column. The reviewer is right. We have added some index to explain the table 2.

Table 2 Univariate analysis of predictors for pancreatic fistula following pancreaticoduodenectomy

Characteristics	POPF occurrence				CR-POPF occurrence			
	Yes	No	*P* value	χ^2 value	Yes	No	*P* value	χ^2 value
Gender			0.429	0.625			0.715	0.134
male	81	41			41	81		
female	45	29			23	51		
Age			0.492	0.471			0.119	2.433
⩾60y	53	33			23	63		
<60y	73	37			41	69		
BMI			0.696	0.153			0.052	3.791
⩾25kg/m^2	38	23			14	47		
<25kg/m^2	88	47			50	85		
Hypertension			0.728	0.121			0.930	0.008
yes	39	20			19	40		
no	87	50			45	92		
Diabetes mellitus			0.431	0.621			0.959	0.003
yes	18	13			10	21		
no	108	57			54	111		
Serum CA19-9			0.257	1.285			0.774	0.082
>37 μ g/L	65	42			34	73		
⩽37 μ g/L	61	28			30	59		
pre-operative jaundice			0.638	0.222			0.147	2.102
yes	71	37			40	68		
no	55	33			24	64		
Serum albumin			0.572	0.319			0.498	0.460
<35g/L	18	8			10	16		
⩾35g/L	108	62			54	116		
Blood loss			0.109	2.576			0.639	0.220
⩾600ml	16	15			9	22		
<600ml	110	55			55	110		
Pancreatic duct diameter			0.000	15.696			0.008	6.952
⩽3mm	75	21			40	56		
>3mm	51	49			24	76		
Pylorus-preserving			0.798	0.066			0.159	1.987
yes	57	33			34	56		
no	69	37			30	76		
Pancreatic drainage			0.800	0.064			0.023	5.180
external	40	21			13	48		
enteral	86	49			51	84		
Pancreatico-jejunostomy			0.307	1.043			0.766	0.089
duct-to-mucosa	117	62			59	120		
invagination	9	8			5	12		

(4) Revision has been made according to the suggestions of the reviewer about table 3.

Table 3 Logistic regression for predictors of pancreatic fistula following pancreaticoduodenectomy

Variables	B	SE	*Wals*	*P* value	*OR*	95% *CI*
Total PF						
Pancreatic duct diameter	-1.233	0.318	15.056	0.000	0.291	0.156-0.543
Clinically relevant PF						
Pancreatic duct diameter	-0.919	0.321	8.171	0.004	0.399	0.213-0.749
Pancreatic drainage	-0.932	0.37	6.339	0.012	0.394	0.191-0.813

To 00159291-reviewer as follows:

1 Page 1. Absrtact-Results: please specify exactly what is the diameter of the duct which influence the fistula rates and how.

A: pancreatic duct diameter ≤3mm was independent risk factor for postoperative pancreatic fistula.

2.Page 4. Line 5: "Three patients died…" should be "All three patients died.."

A: Revision has been made according to the suggestions of the reviewer.

3.Page 4. Line 13: "Two periperative..." should be "Two perioperative…".

A: Revision has been made according to the suggestions of the reviewer.

4.Page 4. Line 17-18: Please clarify what do you mean by external pancreatic juice draining. Also what do you mean in the entire paper by external pancreatic stent? It is not clear! It is an externalized stent through the abdominal wall, jejunum to the pancreatic duct, or just an internal stent from the duct inside the jejunal loop? Please clarify!

A: Revision has been made according to the suggestions of the reviewer.

An external stent across pancreaticojejunal anastomosis through the abdominal wall is used (complete external drainage of the pancreatic juice).

5.Page 5. Discussion line 2: "fetal delayed" should be "fatal delayed".

A: Revision has been made according to the suggestions of the reviewer.

6.Page 5. Discussion. Lines 5-7: "The International Study Group on Pancreatic Fistula Definition (ISGPF) has recently proposed a standardized definition of POPF". Please specify the reference!

A: Revision has been made according to the suggestions of the reviewer.

7.Page 6. Discussion: When mention reference 26 please, again, be very clear and explain what external pancreatic stent, internal, external drainage mean! Even for an expert the way you mentioned could be unclear.

A: Revision has been made according to the suggestions of the reviewer.

8.Page 6. At the end please add that postoperative fistula is also the cause of mortality.

A: Revision has been made according to the suggestions of the reviewer.

The drainage bile and pancreatic secretion separated could reduce the mortality of CR-POPF and alleviate the severity of POPF.

9. Overall please discuss the existent prospective studies in the field which confirmed on the most solid scientific base the role of duct diameter and pancreatic texture. Suggested reference: "Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM Jr. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. J Am Coll Surg. 2013, 216:1-14".

A: Revision has been made according to the suggestions of the reviewer.

Callery et al reported a simple 10-point Fistula Risk Score based on small duct, soft pancreas, high-risk

pathology and excessive blood loss accurately predicts subsequent CR-POPF. It can be readily learned and broadly deployed. This prediction tool can help surgeons anticipate, identify, and manage this ominous complication from the outset.

To 02460781-reviewer as follows:

We have developed to data analysis of all three groups of under and over 70 years old, under and over 65 years old, under and over 60 years old, unfortunately, all of them showed no significance. Finally, we chose one of them as a risk factor.

For patients with periampullary tumor, the RCTs and meta-analyses showed no benefit of preoperative biliary drainage. Instead, there were some concerns about the drainage-related complications and the increase in positive intraoperative bile culture rate and the associated infective complication rate postoperatively. In the Chinese PLA General Hospital, preoperative biliary drainage has not been developed routinely before pancreaticoduodenectomy for patients with periampullary tumor. Furthermore, different level of serum total bilirubin showed no difference on morbidity of postoperative pancreatic fistula following pancreaticoduodenectomy according our study. Accordingly, we chose whether complicated jaundice or not as a risk factor.

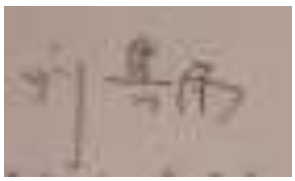
Pancreatic texture was described only in operation record, and it's a subjective one. Unfortunately, pancreatic texture test was not implemented routinely preoperation and the study was lack of objective data.

Creatinine clearance abnormality and coronary artery disease related to morbidity or mortality rate but showed no relation to postoperative pancreatic fistula.

3 References and typesetting were corrected

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

Sincerely yours,



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