Dear Jin-Zhou Tang

Thank you for inviting us to submit a revised draft of our manuscript entitled, "Usefulness of serum lipase for early diagnosis of post-endoscopic retrograde cholangiopancreatography pancreatitis" to World Journal of Gastrointestinal Endoscopy. We also appreciate the time and effort you and each of the reviewers have dedicated to providing insightful feedback on ways to strengthen our paper. Thus, it is with great pleasure that we resubmit our article for further consideration. We have incorporated changes that reflect the detailed suggestions you have graciously provided. We also hope that our edits and responses below satisfactorily address all of the issues and concerns you and the reviewers have noted.

We have added and changed the sentences in accordance with editor's comments. For figures, we have changed a blue and a green line to a solid and a dashed line. We have changed the title of the figure/table. But, it has become long, we can change to a shorter title. For example, in Table2, the title is "Comparison of incidence rates at each stage".

To facilitate your review of our revisions, the following are our point-by-point responses to the questions and comments provided in your email dated August 15, 2019. We have also marked the sentences that were changed according to the reviewer's comments.

2 Peer-review report

Dear reviewer #1

We wish to express our appreciation to the reviewer for their insightful comments on our paper. The comments have helped us significantly improve the paper.

Why were there only 804 cases out of 4192 ERCPs? Were some patients excluded?
We wish to thank the reviewer for this comment. We selected the cases according to the exclusion criteria. These criteria are described in the Materials and Methods section. Examples of excluded cases are as follows:
Treated major duodenal papilla: 2703 cases
Unable to reach major duodenal papilla: 6 cases
Blood test not performed: 245 cases
Cholangiojejunostomy history: 234 cases

Should the study be repeated in a screening setting to determine the results when there was significant pain and when patients were pain free?
It is often difficult to evaluate the presence or absence of spontaneous pain due to the effects of analgesics used in ERCP, particularly in elderly people. Therefore, if hyperlipasemia or hyperamylasemia occurred after ERCP, an imaging test was performed at the discretion of the attending physician. Therefore, even if the abdominal pain was mild, it was determined as PEP if pancreatitis was observed in the image findings.

Many of the references were very old and should be revised in the more modern literature.

Thank you for this suggestion. We have added new references to the paper.

These results are similar to ours (1) in an emergency ward setting where we demonstrated the diagnostic advantage of s.lipase. We presumed the difference in ROC curves was partly because amylase is derived from other organs than the pancreas and that the lipase measure was specific for pancreatic lipase. In the setting of ERCP presumably both enzymes are elevated by damage to the pancreas. So why the difference?

S-Lip has a higher pancreatic specificity and is known to be more useful than s-Amy in acute pancreatitis [1-3]. Similarly, S-Lip may also be more useful than s-Amy for PEP. We have added a sentence stating that S-Lip has a higher pancreatic specificity to the Discussion section.

I am not sure what would be different in the care of patients with elevated enzyme values after ERCP. In our hospital system patients mostly have the ERCP in an outpatient setting. What would be the impact on hospital beds if S. Lipase was used as a screening where mild pancreatic inflammation would be difficult to discern from moderate to severe inflammation?

As a general rule, in our institution, patients are hospitalized on the day of ERCP so that PEP can be diagnosed and therapeutic intervention can be conducted as early as possible. Therefore, it is not possible to make any predictions about the impact on hospital beds in this study.

Dear reviewer #2

We wish to express our appreciation to the reviewer for their insightful comments on our paper. The comments have helped us significantly improve the paper.

Review of: Tadehara et. Al: ”Usefulness of serum lipase for early diagnosis of post-endoscopic retrograde cholangiopancreatography pancreatitis” The study evaluates the usefulness of serum lipase as compared to serum amylase for the early identification of post-ERCP pancreatitis. The study is a retrospective cohort study including 804 ERCP-patients from two Japanese hospitals over a period of five years. The topic is relevant, but certain limitation of the study needs to be addressed.

Major comments: The study uses the Cotton consensus criteria for evaluation of PEP-severity. The cotton consensus criteria is no longer used for evaluation of PEP-severity, since the Revised Atlanta definition has proven far superior. Both the American and European society of Gastrointestinal endoscopy recommends the revised Atlanta for evaluation of PEP-severity. All PEP-cases should be reappraised.

We greatly appreciate the reviewer's comment on this point. We have reclassified severity according to the revised Atlanta criteria.

The statistical analyses aren’t described in detail that ensures reproducibility.

We have added further details on the statistical analysis to the paper.

The numbers for PEP-incidence do not ad up. The authors state that a total of 9.7% (n=78) of the included ERCP patients had a case of PEP. The describe that 40 patients were diagnosed with PEP in the early stage and 38 patients in the late stage. Surely some of the early stage patients are included in the late fase? Or where the patients not evaluated again if they were diagnosed in the early stage? This needs to be clear.

We have added a sentence stating that cases diagnosed with PEP in the early stage were not included for diagnosis in the late stage. After diagnosis of PEP, daily blood tests and image evaluations were performed as needed to observe the severity of PEP and the effects of the course of treatment.

The study included 804 ERCPs – of these 37.7% were on a diagnostic indication. Diagnostic ERCP is not recommended since the risk of PEP overweigh the potential benefits. This needs to be addressed in the discussion since it introduces a bias and reduces transferability to other ERCP centers.

We determined that diagnostic ERCP, such as differential diagnosis of bile duct cancer and benign bile duct stenosis, may still be necessary despite the decrease in use. A prospective study conducted at 11 centers found no significant difference in the incidence of PEP between diagnostic and therapeutic ERCP[4]. Therefore, in this study, we examined all cases to maximize the sample size.

In table 1, it is described that 25.1% and 12.1 % has elevated lipase and amylase

levels before ERCP respectively. These patients should have been excluded, since it remains unconfirmed if these patients actually were developing acute pancreatitis before ERCP or potentially had unconfirmed chronic pancreatitis.

We did in fact exclude cases diagnosed with acute pancreatitis and chronic pancreatitis by imaging. We have added these as exclusion criteria to the Materials and Methods section.

Many of the references used in the introduction does not represent current knowledge. For example, the frequency of PEP is referenced with publications all from the 80s and 90s. Perhaps the authors should read Leerhøy and Elmunzers recent publication How to Avoid Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis for an updated literature review on the topic.

We thank the reviewer for this comment. We have revised the text and references.

The authors evaluated 4192 patients who underwent ERCP, but only included 804 patients. How many of these were because blood tests weren't performed? If this is the main exclusion criteria, it introduces a large selection bias.

We thank the reviewer for this comment. We have added the exclusion criteria to Figure 1. Examples of cases excluded are as follows:

Treated major duodenal papilla: 2703 cases

Unable to reach major duodenal papilla: 6 cases

Blood test not performed: 245 cases

Cholangiojejunostomy history: 234 cases

Minor comments.

Abstract Line 2, change to new onset of acute pancreatitis

In accordance with the reviewer's and native English speaking editor's comment, we have revised the sentence to "new onset acute pancreatitis".

Introduction: Line 2, same as above

We have revised the sentence to "new onset acute pancreatitis".

Line 4, not correct. Both the cotton and Atlanta definition should be mentioned here. Please see ASGE and ESGE guidelines. Regarding frequencies of PEP. The applied numbers and references don't represent current knowledge. These should be updated.

Accordingly, we have described and referred to the consensus criteria and the revised Atlanta criteria. We have changed frequencies of PEP in the Introduction section. We have revised the text and references.

Materials and methods: Line 1, "The subjects were…." change to: A total of 4,192 patients who underwent ERCP…were evaluated for inclusion.

We have changed the sentence to "A total of 4,192 patients who underwent ERCP…were evaluated for inclusion".

Discussion: Line 2, "Our study showed that s-lip is sign more useful than…." Due to the study design this conclusion is not warranted. Change to Our study

indicated that s-lip might be preferable in the early diagnosis of PEP (or similar)

We have changed the sentence to "Our study indicated that s-Lip might be preferable in the early diagnosis of PEP".

Line 5, "More than 50 years…." Delete sentence.

We have deleted this sentence.

Line 10/11, "If PEP is diagnosed early ….which can prevent more severe states".

We do not know if this is true – currently no specific treatment is available.

We have deleted "which can prevent more severe states".

3th to last line page 8, Do you consider a CT scan a highly invasive examination? And why is it warranted? If the patient has elevated enzymes an abdominal pain, they per definition have PEP and should be treated as such.

We have deleted "highly invasive examinations, such as".

2th to last line page 8, change lipase to s-lip

This error has been corrected in accordance with the reviewer's comment.

Page 9 in the limitation section, "…it was a single-center study…" In the method section you describe that you included patients from two hospitals? Futhermore, selection bias needs to be addressed in the discussion.

We have changed the sentence to "…at two centers as a retrospective study…".

We have added further descriptions on the selection bias.

Bottom page 9, conclusion. Due to study design the conclusion needs to be lees affirmative. Perhaps change to: In this study s-lip was more useful than s-amy….
We have changed the sentence to "In this study s-lip was more useful than s-amy….".

Reference List

1. Smith RC, Southwell-Keely J, Chesher D. Should serum pancreatic lipase replace serum amylase as a biomarker of acute pancreatitis? *ANZ J Surg* 2005; 75: 399-404.
2. Treacy J, Williams A, Bais R, et al. Evaluation of amylase and lipase in the diagnosis of acute pancreatitis. *ANZ J Surg* 2001; 71: 577-582.
3. Keim V, Teich N, Fiedler F, et al. A comparison of lipase and amylase in the diagnosis of acute pancreatitis in patients with abdominal pain. *Pancreas* 1998; 16: 45-49.
4. Freeman ML, DiSario JA, Nelson DB, et al. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. *Gastrointest Endosc* 2001; 54: 425-34.

Again, we appreciate all of your insightful comments. We have worked hard to respond to them. Thank you for taking the time to help us improve the paper.

Sincerely yours,

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