Dear Professor Lian-Sheng Ma,
President and Company Editor-in-Chief
Baishideng Publishing Group Co., Limited

Thank you very much for your response regarding our manuscript, "**The Combination of 2 h Post-ERCP Amylase Levels and Cannulation Time is Useful for Predicting Post-ERCP Pancreatitis"**. We have carefully read the reviewers' comments and revised the manuscript in accordance with their suggestions.

We have attached point-by-point responses to the reviewers' comments for your convenience. We modified the manuscript using "track changes" mode in Word and have asked a copy-editing company to correct its grammar and syntax errors.

We sincerely hope that the revised manuscript is acceptable for publication in ***World Journal of Gastrointestinal Endoscopy***.

All authors accept responsibility for the content of the manuscript and satisfy the requirements for authorship.

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Sincerely,

Tsutomu Nishida, M.D., Ph.D.

Responses to Reviewer *03479389*'s comments

Thank you very much for your valuable and constructive comments regarding our manuscript. We believe that your comments have enabled us to significantly improve the manuscript.

Our responses to your comments are as follows:

1. **I expect the reanalysis of PEP in patients with a naïve papilla of Vater.**

   Thank you for your constructive suggestion. We considered 'naïve papilla' a PEP risk factor. Univariate analysis demonstrated that a naïve papilla was a significant PEP risk factor, whereas multivariate analysis demonstrated that a naïve papilla was not a significant PEP risk factor. We reanalyzed the naïve papilla cases (N=688) as you suggested and observed that the cannulation time, procedure time and 2 h amylase cutoff levels for those cases were 13 min, 55 min and 264 IU/L, respectively, and were thus similar to those for all other cases, which convinced us of the validity of those numerical cutoffs with respect to predicting PEP. We have inserted the following sentences into the revised manuscript on page 12, line 5 (a) and page 13, line 4 (b):

   (a) A total of 688 patients (59%) exhibited naive papillae.
   (b) and remained 264 IU/L when limited to naïve papilla cases (n=688).
   (Figure 2) and remained 264 IU/L when limited to naïve papilla cases (n=688).

2. **In PEP cases with 2 h amylase levels greater than the cutoff level how many cases are there in patients required more than 13 minutes for the cannulation?**

   Thank you for this comment. Twenty-eight cases with 2 h amylase levels greater than the cutoff required more than 13 minutes for cannulation in the present study. In accordance with your comment, we revised Figure 3 to include this information.

3. **What kind of protease inhibitor did you use? Please describe the dose of protease inhibitor.**

   Thank you for this advice. We have included the name and dose of the protease inhibitor (200 mg gabexate mesilate x2/day) on page 8, lines 13-14, of the revised manuscript, in accordance with your suggestion.

4. **How many patients did you use the pancreatic stent to prevent pancreatitis? In the pancreatic stent placement cases, please investigate the analysis of PEP**

Thank you for this suggestion. Prophylactic pancreatic stents were placed in 124 patients in the present study, 9 of whom (7.3%) developed PEP. However, multivariate analysis demonstrated that stent placement did not significantly prevent PEP, perhaps because pancreatic stents tend to be used in patients at high risk for PEP, in accordance with the above guidelines. Therefore, we must target patients at high risk for PEP to evaluate the efficacy of prophylactic pancreatic stent placement. We believe that these points are important and have therefore added the following the sentences to the revised manuscript (page 20, line 8):

> In addition, the ESGE guidelines recommend that prophylactic pancreatic stent placement should be strongly considered in patients at high risk for PEP. Prophylactic pancreatic stents were placed in 124 patients in the present study, 9 of whom (7.3%) developed PEP. However, multivariate analysis demonstrated that stent placement did not significantly prevent PEP, perhaps because pancreatic stents tend to be used in patients at high risk for PEP, in accordance with the above guidelines. Therefore, we must target patients at high risk for PEP to evaluate the efficacy of prophylactic pancreatic stent placement.

Thank you very much. We hope that the revised manuscript is acceptable for publication in ***World Journal of Gastrointestinal Endoscopy***.

Responses to Reviewer *03026750*'s comments

Thank you very much for your valuable and constructive comments regarding our manuscript. We believe that your comments have enabled us to significantly improve the manuscript.

Our responses to your comments are as follows:

1. **Although the study does not add too much, the manuscript is generally well written, and drawbacks were mentioned in study limitations**

   Thank you for your helpful comment. As you indicated, the study does not add much new information; however, we believe that our analysis of 2 h post-ERCP amylase levels will contribute to PEP treatment research in the future.

Thank you very much. We hope that the revised manuscript is acceptable for publication in ***World Journal of Gastrointestinal Endoscopy***.

Responses to Reviewer *03474672's* comments

Thank you very much for your valuable and constructive comments regarding our manuscript. We believe that your comments have enabled us to significantly improve the manuscript.

Our responses to your comments are as follows:

1. **What kind of protease inhibitor was used? Please describe, dose and name them.**

   Thank you for this advice. We have included the name and dose of the protease inhibitor (200 mg gabexate mesilate x2/day) on page 8, lines 13-14, of the revised manuscript, in accordance with your suggestion.

2. **In the Table 1: Patient characteristics, I suggest that the "others" ERCP indications could be more specific (name at least three more expressive causes) since it corresponded with 30% of your sample.**

   Thank you. We have revised the following sentence in the revised manuscript (page 12, lines 7-10) and modified Table 1 in accordance with your suggestion:

   ERCP was performed for choledocholithiasis (n=771); biliary malignancies from pancreatic cancer (n=203); biliary malignancies from common bile duct cancer (n=161); other biliary malignancies, including gallbladder cancer, intrahepatic bile duct cancer and other metastatic cancers (n=158); and other conditions (n=110).

3. **Another important piece of information is to mention in the method if the ERCP procedures were performed by expert endoscopists or fellows. Is your hospital a teaching hospital? It would be interesting if the authors could considerer these suggestions.**

   Thank you for your constructive suggestions. Our facility is located in Japan and is a Japan Gastroenterological Endoscopy Society (No.1239)-certified teaching hospital. Our hospital does not have specific rules regarding the performance of ERCP, but trainee endoscopists must perform more than 1000 regular esophagogastroduodenoscopies (EGDs) and 1000 colonoscopies before beginning ERCP procedures. Moreover, all trainee endoscopists are assisted by experienced endoscopist when performing ERCP procedures in case of procedural difficulty.

   We have inserted the following sentences into the revised manuscript on page 7, line 5 (a) and page 8, line 5(b):

(a) certified as a teaching hospital by the Japan Gastroenterological Endoscopy Society (No. 1239)
(b) Trainees or experts performed ERCP because our hospital is a JGES-certified teaching hospital, and trainees were assisted by experts as needed to avoid complications and ensure procedural quality when performing ERPC.

Thank you very much. We hope that the revised manuscript is acceptable for publication in ***World Journal of Gastrointestinal Endoscopy***.

Responses to Reviewer *03475242's* comments

Thank you very much for your valuable and constructive comments regarding our manuscript. We believe that your comments have enabled us to significantly improve the manuscript.

Our responses to your comments are as follows:

1. **(1) This is a retrospective cohort study, but please explain the reason why more than 90% of the patients could have serum levels of amylase measured at 2 hour after procedure. Do you have a special protocol in the performance of ERCP?**

   Thank you for your question. Our ERCP protocol requires that amylase levels are measured 2 h post-procedure and the following morning, except in patients who have already developed pancreatitis. We have added the following sentence to the revised manuscript on page 8, lines 11-12:

   Patients underwent routine blood tests 2 h after the procedure and the following day

2. **(2) In your hospital, how could precise records of cannulation time and procedure time be obtained?. For each ERCP procedure, were these times recorded by a nurse or doctor?**

   Thank you for your question. We routinely measured procedure times using a stopwatch and recorded images at key points. Unfortunately, some data are missing due to the retrospective study of this study. We have added the following sentence to the Methods section of the revised manuscript (page 8, lines 9-11):

   Procedure times were measured using a stopwatch, and images were recorded at key points and subsequently reviewed.

3. **(3) This paper studied 1,403 procedures in 725 patients who underwent ERCP. Therefore, on an average, each patient received ERCP twice. This study cohort included repeat-ERCP patients in more than half of the study group. I think therefore that the authors should add repeated time of ERPC as one of risk factor analysis. Anyway, you added the factor of naive papilla.**

   Thank you for your constructive suggestion. We completely agree with your comment. We considered 'repeat ERCP' a PEP risk factor. Univariate analysis

demonstrated that a naïve papilla was a significant PEP risk factor, whereas multivariate analysis demonstrated that a naïve papilla was not a significant PEP risk factor. We reanalyzed the naïve papilla cases (N=688) as you suggested and observed that the cannulation time, procedure time and 2 h amylase cutoff levels for those cases were 13 min, 55 min and 264 IU/L, respectively, and were thus similar to those for all other cases, which convinced us of the validity of those numerical cutoffs with respect to predicting PEP. We have inserted the following sentences into the revised manuscript on page 12, line 5 (a) and page 13, line 4 (b):

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(b) and remained 264 IU/L when limited to naïve papilla cases (n=688).
(Figure 2) and remained 264 IU/L when limited to naïve papilla cases (n=688).

Thank you very much. We hope that the revised manuscript is acceptable for publication in ***World Journal of Gastrointestinal Endoscopy***.

Responses to Reviewer *01438494*'s comments

Thank you very much for your comments regarding our manuscript. We would be very happy if the revised manuscript were found acceptable for publication in ***World Journal of Gastrointestinal Endoscopy.***

1. **To conclude that 2 times value of amylase 2 hours after ERCP is considered to be the threshold of PEP is interesting. This paper is worth to be read for clinician of pancreatobiliary disorders.**

   We are very grateful for your helpful comment. Thank you.

Responses to Reviewer *03476646*'s comments

Thank you very much for your valuable and constructive comments regarding our manuscript. We believe that your comments have enabled us to significantly improve the manuscript.

Our responses to your comments are as follows:

1. **This study lacked of 117 procedures with the following conditions were excluded: 1) gallstone pancreatitis, 2) unreachable to papilla, and 3) missing data of procedure time or serum amylase levels. Thus this study may have low confidence level. And the contents of this manuscript may have low impact.**

   Thank you for your suggestion. We agree with the limitations noted above. Our cohort included patients who had already developed pancreatitis (n=17), as well as patients with unreachable papillae (n=40) and patients with missing data (n=60). The cases with missing data represented 3.9% (60/1520) of the study and included some patients with pancreatitis. The endoscopists who treated these patients determined that 2 h post-ERCP levels were unnecessary. We have added the following sentence to the revised manuscript on page 7, line 8:

   1) gallstone pancreatitis, n=17; 2) unreachable papillae, n=40; and 3) missing procedure time or serum amylase level data, n=60 (including cases with pancreatitis before ERCP).

2. **Major 1: The similar sentences of the contents "Andriulli et al. reported a systematic… However, very few good positive predictive values (PPVs) for PEP exist." is described on discussion. It seems persistently. Thus, Those may be better that those sentences of the contents are described on only discussion or introduction.**

   Thank you for your suggestion. We have deleted these sentences and shortened the Introduction.

3. **Major 2: Did you compare between contrast method and wire-guided method, and consider the details included of complications? If you didn't, the sentence that there is no difference of the PEP incidence in contrast method and WG method may be better to be added to the text and reference.**

   Thank you for your suggestion. We agree with your comments and would have

preferred to analyze the cannulation methods. Unfortunately, it is difficult to compare contrast and wire-guided cannulation, as our institution does not have a strict cannulation protocol. However, most of the procedures were initiated using the 'wire-loaded' method, and changes were made as needed at the discretion of the treating physician(s). However, your point is very important. We have therefore revised the following sentence in the revised manuscript (page 8 line 7):

批注 [ED1]: Please ensure that the intended meaning has been maintained in this edit.

We did not use a strict cannulation protocol. Cannulation was attempted via the wire-loaded cannulation method, which entails the use of contrast and wire-guided cannulation using a side-viewing duodenoscope.

4. **Minor 1: The word of "occurs" (on page 5, line 21) should be changed to "occurred".**

   We have revised "occurs" to "occurred" in accordance with your suggestion.

5. **Minor 2: You wrote the sentence "Many studies have investigated the factors that increase the risk of post-ERCP pancreatitis." On page 6 line 1. If so, some references should be shown.**

   We have added the appropriate references in accordance with your comment.

6. **Minor 3: The mean of EBS on Table 3 is EBS without EST?**

   Thank you for your question. EBS was performed both with and without EST (27%, or 104/380 EBS procedures, were performed with EST). We have added the indicated information [* EBS: including with and without EST] to Table 3.

Thank you very much. We hope that the revised manuscript is acceptable for publication in ***World Journal of Gastrointestinal Endoscopy***.