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August 16, 2013

Dear Professor Lian-Sheng Ma
President and Editor-in-Chief "**World Journal of Gastroenterology**"
Dear Jin-Lei Wang, Director,

Thank you for your kind letter concerning our manuscript entitled "**Risk factors to predict severe postoperative pancreatic fistula following gastrectomy for gastric cancer y (Ms: wjg/2013/3920)**" by Komatsu et al. We have revised the manuscript according to reviewer's comments using a red color font (highlighted revise version) and presented the outlining responses to your comments below.

We thank you for the valuable suggestions and comments for the manuscript. We have carefully revised it accordingly. Explanations have been provided point by point. We believe that our revised manuscript has been improved by these revisions, and satisfy your concerns. We cordially appreciate your work regarding our manuscript. We hope that the revised manuscript is now acceptable for publication in the "**World Journal of Gastroenterology**".

Sincerely yours,

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Comments to authors from editor

Your manuscript (**ESPS Manuscript NO: 3920**) entitled "Title: **Risk factors to predict severe postoperative pancreatic fistula following gastrectomy for gastric cancer**", which you submitted to **World Journal of Gastroenterology**, has been reviewed. Please find the reviewers' comments online at our website: http://www.wjgnet.com/esps/.

Based on the reviewers' comments, your manuscript could be accepted for publication should you be prepared to incorporate revisions. When preparing your revised manuscript, you are asked to address the points raised by the reviewers and revise your manuscript accordingly to meet the standards and format of **World Journal of Gastroenterology**.

Response to editor's comments

Thank you for your kind and promising letter concerning our manuscript. We have revised the manuscript according to reviewer's comments as follows. We believe that our revised manuscript have been improved by revisions, and satisfy your concerns. We cordially appreciate your work regarding our manuscript. We hope that the revised manuscript is now acceptable for publication in "**World Journal of Gastroenterology**".

Reviewer #1:
Reviewer code: 00058054
Date reviewed: 2013-06-26 17:27

Comments to Authors:
In this manuscript, authors have analyzed the clinical data of patients with POPF following gastrectomy for gastric cancer, retrospectively. Authors concluded that ISGPF classification was applicable to POPF as a complication of gastrectomy and lower lymphocyte counts at the diagnosis of POPF was the independent risk factor of Grade C POPF. Basically, this paper is well written and the results are interesting for readers, however, several issues should be clarified.

Response to reviewer#1's comments
Thank you for your kind comments. We cordially appreciate your contribution to the review of our manuscript and found them to be great helpful. We have revised our manuscript accordingly. We hope that our manuscript has been more improved by these revisions and that we have adequately addressed your concerns.

Query
1. As authors mentioned, a low lymphocyte count is changeable by the timing of diagnosis of POPF. Therefore, it seems not to be a cause but to be a result of severe POPF. How should we use this factor to prevent severe POPF? Please discuss in Discussion section.

Reply
Thank you for your reasonable comment. As you indicated, a low lymphocyte count is not a causative factor to be extremely severe grade C POPF, but it is 'predictive' factor for grade C POPF. Therefore, it is not possible to prevent severe POPF, but is possible to predict severe POPF at the disease process of POPF and start intensive treatment earlier.

At first, we hypothesized that there were some differences among the previously reported risk factors associated with the occurrence of POPF between grade B and C in patients with POPF. However, contrary to our expectations, there was no correlation with the previously reported factors. Therefore, next, we hypothesized that there were predictive factors which provide an objective description of the patient's condition at specific points in the disease process of POPF, which are useful to improve understanding of the complications that may be encountered. Indeed, to date, after patients develop POPF, there are no generally accepted risk factors to predict these patients to change extremely severe POPF. These comments were also written in Discussion, paragraph 4.

In this study, we detected a risk factor to predict extremely severe POPF in the disease process of POPF. No surgeons could avoid all POPF because intensive lymphadenectomy for cure of gastric cancer might have a potential risk for POPF. If POPF was developed, next, early diagnosis for extremely severe POPF and starting appropriate treatment would be more important than preventing all POPF. Therefore, we believe that a lower lymphocyte count could provide an objective description and is useful for understanding the complications that may be encountered. Thank you for your reasonable comments.

Query

2. Authors should explain intensive POPF treatments in detail.

Reply

Thank you for your comments. The content of intensive POPF treatment strategy is very important for overcoming severe POPF. Previous review articles have already reported it and this paper is not a review paper for POPF treatments, however, we added our treatment strategy for sever POPF treatments briefly and revised **Patients and Methods** as follows.

Revised version

Treatment strategy for POPF following gastrectomy

Patients with POPF, which is diagnosed by high D-AMY level and have no abnormal physical finding and laboratory data, could be followed without any treatments. Abdominal drainage tube is normally removed after changing the D-AMY level into the lower level than three times of serum AMY level. Patients with POPF, which is diagnosed by high D-AMY level and have abnormal findings such as fever, abdominal pain and other laboratory data, would start to undergo intensive POPF treatments. Namely, after emergency CT examination, if drainage tube position was good, antibiotics, octreotide acetate and total parenteral nutrition would be started. If fluid drainage tube position was not satisfactory, additional or alternative drainage tube would be placed into abnormal fluid cavity by percutaneous CT or ultrasonography-guided technique. Moreover, bacterial infection of drainage fluid and/or the suspicion of it were detected following these POPF treatments, drainage tube would be changed into irrigation type drainage tube. Then, continuous irrigation and drainage with saline would be performed. If these series of conservative POPF treatments were not effective, open drainage and debridement for POPF abscess by laparotomy would be performed and irrigation type drainage tube and enteral feeding tube would be placed. Then, comprehensive POPF treatments consist of continuous irrigation drainage with saline, antibiotics, octreotide acetate and enteral nutrition would be performed.

Reviewer #2:
Reviewer code: 01503696
Date reviewed: 2013-06-13 18:02

Comments to Authors:
Post-operative pancreatic fistula (POPF) is a clinically important issue in gastric cancer surgery. It has a value to identify risk factors for POPF. Komatsu and colleague tried to identify risk factors in patients who were diagnosed with Grade B or Grade C POPF, and found that Grade B or C was significantly correlated with treatment duration.

Response to reviewer#2's comments
Thank you for your kind comments. We cordially appreciate your contribution to the review of our manuscript and found them to be great helpful. We have revised our manuscript accordingly. We hope that our manuscript has been more improved by these revisions and that we have adequately addressed your concerns.

Query
The aim of the study is clear but the method is not appropriate. Authors seem to be interested in the treatment duration and performed correlation analysis. However, the result is not surprising because Grade B or Grade C is determined by considering the treatment duration itself. Only interesting point is that age and lymphocyte count were significant independent risk factors for Grade C. However, age and lymphocyte count were not correlated with treatment duration.

Reply
Thank you for your reasonable comments. In this study, we did not define POPF grade by using the treatment duration itself. As you already know, the factor of drainage duration is included in POPF grading and this factor also can define both grade B and C POPF as same category (Bassi C 2005, Surgery). Moreover, the treatment duration was not reported to be associated with the difference between grade B and C POPF. However, as you indicated, we also agree that it is not surprising that longer treatment duration is associated with more severe POPF.

Originally, ISGPF classification is invented to define the POPF grading for pancreatic resection. We think that it is worthy that ISGPF POPF grading is also reflecting the treatment duration of POPF following gastrectomy, which its POPF is mainly caused by lymphadenectomy and splenectomy.

Concerning reasons that age and lymphocyte count were not correlated with treatment duration although a lymphocyte count was significant independent predictive factors for Grade C, the treatment duration is one of indicators in the severity of POPF. Whereas, POPF grading, which defined by ISGPF, is comprehensive indicator in the severity of POPF. As you may understand under detail consideration, we think it is not surprising that age and lymphocyte count were not correlated with treatment duration, although POPF grading was associated with treatment duration.

Thank you for your helpful and reasonable comments. If you have any further comments, we are willing to answer and discuss them. We found your comments most valuable and cordially appreciate your concerns and contributions for review of our manuscript. Thank you.

Reviewer #3:
Reviewer code: 1557283
Date reviewed: 2013-06-08 10:52

Comments to Authors:
The present study reported by Dr. KOMATSU et al. investigated the risk factors of POPF according to the ISGPF after gastrectomy in a large number of patients with gastric cancer. They newly found that the lower lymphocyte count at the diagnosis of POPF was significantly associated with POPF. The article was nicely summarized but some modifications may improve the importance of the article.

Response to reviewer#3's comments
Thank you for your kind comments. We cordially appreciate your contribution to the review of our manuscript and found them to be great helpful. We have revised our manuscript accordingly. We hope that our manuscript has been more improved by these revisions and that we have adequately addressed your concerns.

Major comments:
Query
1. One of the important comments was that the lower lymphocyte count at the diagnosis of POPF does not seem predictive but natural. Indeed, lymphocyte count naturally decreases in patients with high grade complications. Was not the lymphocyte count before gastrectomy associated with POPF?

Reply
Thank you for your reasonable comments. As you indicated that lymphocyte count naturally decreases in patients with high grade complications, your comment is very important for this study. Patients with POPF, which have only abnormal D-AMY data, can be followed without any treatment. These patients mainly resulted in grade A POPF; however, some of these patients may later develop severe POPF. As experienced gastric surgeons including you and us have already known, severe POPF sometimes presents no clinical symptoms such as high grade fever and abdominal pain until some time later. Therefore, in this study, we examined predictive indicators which provide an objective description of the patient's condition at specific points in the disease process of POPF, which are useful to improve understanding of the complications that may be encountered. Indeed, to date, there are no generally accepted risk factors to predict the POPF to change extremely severe POPF after patients develop POPF. Therefore, we think that independent predictive factor such as lymphocyte count for severe POPF is very important during POPF treatments.

Concerning preoperative lymphocyte count, in this study, there was no association with grade C POPF (data not shown). However, after this study, we prospectively determined predictive effect of preoperative lymphocyte count. Consequently, preoperative lymphocyte count not distinguish between grade B and C POPF as same as the result of this study. These prospective study results are currently under evaluation and we will repot it in near future. Thank you for your helpful comments.

Query

2. In the Table 2 the authors divided into two groups at 1400/mm3 of the lymphocyte count before gastrectomy, and they also divided into two groups at 1400/mm3 after gastrectomy. The cut-off values before as well as after gastrectomy do not seem appropriate. The authors should show p-values of the ROC curve concerning pre- and post-operative lymphocyte counts in their point-by-point responses.

Reply

Thank you for your important comments. In both **Table 2** and **Table 3**, a lymphocyte count was the data at the diagnosis of POPF. We revised the annotation of 'lymphocyte count' into 'lymphocyte count at the diagnosis of POPF in both **Table 2** and **Table 3**.

The cut-off value of 1400/mm3 is calculated by the ROC-curve to distinguish between grade B and C POPF. Therefore, we used this value in **Table 3** and added the ROC-curve in the **Supplementary Figure 1** . Regarding **Table 2,** we have to detect cu-off value of a lymphocyte count using ROC-curve to distinguish intensive treatment periods between less than 20days and 20days and more. Also, we have to revise p-values accordingly. As a result, the cut-off value of 850/mm3 and area under ROC-curve (AUC) of 0.5181 were calculated by the ROC-curve and p-value was 0.073. We revised **Table 2** and **Table 3.** Thank you for your helpful comments.

Query

3. The Table 3 summarized the factors associated with POPF. Further information may be needed, e.g., sex, reconstruction methods, preoperative co-morbidity, drain-amylase value on the Post-Operative-Day 1, etc. In addition, were not there any patients undergoing laparoscopic gastrectomy in the present study? As shown above, the authors should make an effort to find additional predictive risk factors of POPF in their data base.

Reply

Thank you for your reasonable comments. As you suggested, we already made every effort to find additional predictive risk factor of severe POPF. As you can easily understand, we could not present all examined factors because **table 3** might be so busy. Therefore, we selected more presumable factors for severe POPF. However, we added the information of sex in **table 2** and **3** because it was included in **table 1.**

Concerning other factors which we examined, we added the comments in **Results** as follows. If you think that we should present this information in supplementary table, please let me know to add it to this paper although there were no factors to present clinical impact. Regarding drain-amylase value on the Post-Operative-Day1, previously, we did not routinely measure D-AMY on the Post-Operative-Day 1. Therefore, there were few data to calculate statically because only 35 patients (2.6%) were diagnosed with severe Grade B or C POPF between 1997 and 2010. As for patients who undergo laparoscopic surgery, only one patient developed grade C POPF and was included in this study. Thank you for your helpful comments.

<u>Revised version</u>

In results, paragraph 3, L5,

The incidence of other clinical factors, which were presented in Table 3 and others such as underling disease, methods of reconstruction, HbA1c, postoperative Hb, Alb, preoperative serum total protein, total cholesterol, triglyceride, %VC and FEV1.0% etc., did not significantly differ between both groups.

Query

4. The authors may need to show the incidences of anastomotic leak, intra-abdominal abscess, and other severe complications of Grade 3a or greater according to the Dindo-Clavien classification. Because the authors showed an important report of POPF after gastrectomy, they may have a nice chance to review recent articles concerning POPF after gastrectomy as below. Authors No. of cases Incidence of PF (Grade B or C) Risk Factors of PF Miyai, et al1 277 4% Age, D-Amylase on POD1, Retrieved lymph nodes, BMI, operative time Miki et al2 104 22% sex, body mass index, D-Amylase on POD1 Jiang et al3 798 4.5% sex, BMI, intraoperative blood loss Nobuoka, et al4 740 18% BMI, pancreaticosplenectomy References: 1. Miyai H, Hara M, Hayakawa T, et al: Establishment of a simple predictive scoring system for pancreatic fistula after laparoscopy-assisted gastrectomy. Dig Endosc, 2013 2. Miki Y, Tokunaga M, Bando E, et al: Evaluation of postoperative pancreatic fistula after total gastrectomy with D2 lymphadenectomy by ISGPF classification. J Gastrointest Surg 15:1969-76, 2011 3. Jiang X, Hiki N, Nunobe S, et al: Postoperative pancreatic fistula and the risk factors of laparoscopy-assisted distal gastrectomy for early gastric cancer. Ann Surg Oncol 19:115-21, 2012 4. Nobuoka D, Gotohda N, Konishi M, et al: Prevention of postoperative pancreatic fistula after total gastrectomy. World J Surg 32:2261-6, 2008

Reply

Thank you for your reasonable. In this study, we selected patients with grade B and C POPF, which could be strictly distinguished between POPF and other complications such as anastomotic leakage and intra-abdominal abscess. Concerning the incidence of grade B and C POPF, we reviewed the articles, which POPF was examined by the same definition using ISGPF classification (Obama 5.1 %(12/233), Miki 22.1%(23/104), Jiang X 4.2%(34/798), Miyai H 3.9%(11/277)) and added the comment in Discussion as follows. Thank you for your helpful comments.

Revised version

In discussion, paragraph 1,

Until recently, there has been no universally recognized definition of POPF following gastrectomy for gastric cancer. Accordingly, different definitions of POPF have been reported, which has resulted in highly variable rates of POPF, ranging from 5.8 % to 49.7 %.[7,10,16-20] Therefore, it is impossible to accurately evaluate the incidence and severity of POPF. Obama et al. were the first to utilize the ISGPF classification, which was formulated as an objective definition of POPF following pancreatic surgery in 2005, [15] to evaluate the feasibility of laparoscopic gastrectomy with radical lymphadenectomy for gastric cancer. The incidence of ISGPF grade B or C including both open and laparoscopic gastrectomy was 5.1% (12/233).[21] Miki et al. also reported using the ISGPF classification that a high content of drain AMY on 1POD could be used to predict severe POPF. The

incidence of ISGPF grade B or C following total gastrectomy with D2 lymphadenectomy was 22.1% (23/104). [22] Jiang X et al. recently reported that severe POPF, defined as ISGPF grade B or C, was associated with being male and a high BMI in patients undergoing laparoscopic gastrectomy for gastric cancer. The incidence of ISGPF grade B or C following laparoscopic distal gastrectomy for early gastric cancer was 4.2% (34/798).[11] Miyai et al. advocated that simple predictive scoring system might be useful for many clinicians to assess the risk of POPF after laparoscopic gastrectomy (LAG). The incidence of ISGPF grade B or C following LAG was 3.9% (11/277). [23] These reports clarified the significance of using the same definition of POPF and detecting the risk factors of POPF using the ISGPF classification. However, it remains unclear whether the ISGPF classification following pancreatic surgery can be applied to POPF following gastrectomy to reflect the extent of the severity of POPF and treatment outcomes.

If you have any further comments, we are willing to answer and discuss them. We found your comments most valuable and cordially appreciate your concerns and contributions for review of our manuscript. Thank you.