

3 March 2020

Dear professor:

We greatly appreciate the careful review and comments from you and the reviewers regarding our manuscript. We have made point-by-point responses to each comment in the attached document and have revised our manuscript accordingly.

We believe that with the suggested changes, we have a stronger manuscript for the Journal. We look forward to your positive reply to the revised manuscript.

This manuscript has not been published before, nor is it being considered for publication elsewhere in any language. All authors have read the manuscript and approve its submission to the *World Journal of Gastroenterology*. Please do not hesitate to contact us if we can be of any further assistance.

Sincerely,

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Point-by-point responses: The comments have been carefully taken into account and a new revised submission has been uploaded. We highlighted all the altered passages in yellow in the revised manuscript.

Reviewer 1 :

Overall comments: The authors report occurrence of endocrine dysfunction in 361 patients of acute pancreatitis. They found 41.6% of their patients to have either diabetes or glucose intolerance. The study has a large number of patients with up to 7 years follow up.

Specific comments:

1. What were the co-morbidities; how many patients had pre-existent diabetes.

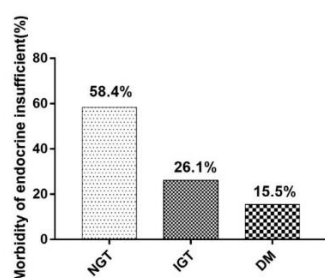
Response(What were the co-morbidities):

Thank you for your suggestion. As is well known, the co-morbidities of diabetes are highly disabling diseases which bring great mental and economic burden to the population. However, we originally designed this study to survey the incidence of diabetes and once it happens, AP patients were allowed to stop follow-up. Hence, we did not observe the occurrence of co-morbidities of diabetes. Subsequently, we would take your advice to investigate the incidence of co-morbidities of diabetes in further study.

Response (how many patients had pre-existent diabetes)

Thank you for your suggestion. We did not clearly describe the part of prediabetes in the manuscript before, but now we have modified and added this part in the Results section. In this study, prediabetes (IGT) and diabetes occurred in 26.1% and 15.5% of all patients after AP onset respectively. The results were shown in the Figure and the morbidity of pancreatic endocrine insufficiency after AP onset were described in the Results section as follows:

94 patients (26.1%) were diagnosed with IGT, 56 patients (15.5%) were diagnosed with DM, and 211 patients (58.4%) were diagnosed with normal glucose.



However, we did not observe the incidence of pre-existent diabetes because one of

the exclusion criteria in this study was AP patients with diabetes or impaired glucose tolerance(IGT). Hence, in future study, it is necessary for us to accept your suggestion to study the difference between AP with pre-existent diabetes and AP patients.

2. Did the authors correlate length of follow up with dysglycemia. from the data give it seems that patients with a follow up of less than one year had the highest prevalence of DM. Do the authors think that there could be beta cell regeneration on a longer follow up? The authors need to compare tests used by them for detecting glycemia with those used in previous studies.

Response: Yes, thank you for your suggestions. In this study, the follow-up time was associated with dysglycemia. As suggested, we have compared our results with previous studies and added the result and discussion sections in the revised manuscript as follows:

Results: Seventy (46.7%) patients who were followed up for 3 months to 1 year, 42 (28.0%) patients who were followed up for 1 year to 3 years, and 38 (25.3%) patients who were followed up for 3 years to 7 years experienced dysglycemia. (Line 152-155 in revised manuscript)

Time of follow up	All patients(n=361)	Normal glucose group (n=211)	Dysglycemia group (n=150)
3M-1Y	211(58.4%)	141(66.8%)	70(46.7%)
1Y-3Y	91(25.2%)	49(23.2%)	42(28.0%)
3Y-7Y	59(16.3%)	21(10.0%)	38(25.3%)

Discussion: Some previous studies have shown that high blood glucose recovers to normal levels soon as the disease improves. This opinion is similar to our finding that patients who were followed up for 3 months to 1 year after discharge experienced dysglycemia more frequently than patients who were followed up for 1 year to 7 years after discharge. We speculated that the recovery of pancreatic function is associated with beta cell regeneration over time. However, another study reported that patients could not fully recover from hyperglycemia and that hyperglycemia could occur again after a short recovery time, even leading to the development of DM and the need for lifelong treatment with drugs or insulin, but they could not confirm whether this effect resulted from the disease or the natural course.

References:

1. Garber AJ, Handelsman Y, Einhorn D, Bergman DA, Bloomgarden ZT, Fonseca V, Garvey WT, Gavin JR, Grunberger G, Horton ES, Jellinger PS, Jones KL, Lebovitz H, Levy P, McGuire DK and Moghissi ES, et al. Diagnosis and management of prediabetes in the continuum of hyperglycemia: when do the risks of diabetes begin? A consensus statement from the American College of Endocrinology and the American Association of Clinical Endocrinologists. ENDOCR PRACT. 2008; 14(7):933-946.
2. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V and Uusitupa M. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001; 344(18):1343-1350.

3. The discussion should be focused only on their results pertaining to aims of the study, there is little point in discussing etiology or proportion of mild disease.

Response: As suggested, I revised the part of the discussion about the proportion of mild disease. Regarding the etiology, I shortened this section and discussed it only briefly at the end of the article.

Reviewer 2 :

Overall comments: The topic is interesting and I think this would be of interest of the readers of World Journal of Gastroenterology.

Specific comments:

1. **First of all, there are so many grammatical errors and immature sentences that are difficult to know the correct meaning throughout the abstract and main text. You had better consult a professional scientific editing service. You had better consult a professional scientific editing service.**

Response: As suggested, I have revised the article and sent it to a professional scientific editing service for modification. I will provide the language certificate to the publishing house.

2. Add 'multivariate analysis revealed' in Results so that it readers can know that it refers to independent risk factors of endocrine pancreatic insufficiency after acute pancreatitis.

Response: As suggested, we have added it in the revised manuscript as follows:

The results of multivariate Cox regression analyses showed that the severity of AP and pancreatic necrosis were independent risk factors for pancreatic endocrine insufficiency in AP patients.

3. 'The area' of pancreatic necrosis is not mentioned in Result.

Response: As suggested, we have supplemented the Results section in the revised manuscript as follows:

According to the CT images, the area of pancreatic necrosis was also divided into 3 subgroups on the basis of the extent of pancreatic necrosis: necrotic area<30%, necrotic area 30%-50% and necrotic area>50%.