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Dear Editor:

Please find enclosed the edited manuscript in Word format (file name: 39693-Revised Manuscript. docx).

Title: Portosplenomesenteric vein thrombosis in patients with early-stage severe acute pancreatitis

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The manuscript has been improved according to the suggestions of the reviewers:
1 Format has been updated
2 Revisions have been made according to the suggestions of the reviewers

Reviewer 1
The authors present an in-depth analysis of the portosplenomesenteric vein thrombosis (PVT) in patients with early-stage severe acute pancreatitis.They identify that incidence of PVT was 17.86%, the independent risk factors were high Balthazar's CTSI scores, hypoalbuminemia and inflammation in the GIT. Furthermore, it is suggested that early drainage and correcting hypoalbuminemia during the early stage of SAP may help prevent the occurrence of PVT. A few comments on the shortcomings:

Comment 1: Definitions of SAP Page 10: "SAP is defined by persistent organ failure, that is, organ failure for longer than 48 h[14].", And the reference 14 is "14 Vikram R, Balachandran A, Bhosale PR, Tamm EP, Marcal LP, Charnsangavej C. Pancreas: peritoneal reflections, ligamentous connections, and pathways of disease spread. Radiographics 2009; 29: e34 [PMID: 19168761 DOI: 10.1148/rg.e34]". The definitions of SAP has an important criteria, the Atlanta classsification in 2012. It is else appeared in the reference 13 in the manuscript. Why do you not use the Atlanta criteria in 2012, and use a old criteria in 2009 ?

Response: Thank you for your comment. SAP was defined by persistent organ failure according to the Atlanta classification in 2012 (page 9). I apologize for

my mistake. I revised this reference.

Comment 2: Case inclusion criteria: The definitions of "early-stage severe acute pancreatitis" is the most important inclusion criteria in the research, but the definition of "early-stage" was not found in the whole article. Only a Exclusion criteria was found in page 8, i.e.,"admission >6 days after AP onset". So, I can only draw a conclusion by inference that the early-stage means ≤6 days after SAP onset (note: the acronyms is AP in the Page 8 and Page 14, but the acronyms of SAP is more rigorous). Moreover, according to the Atlanta classsification in 2012, "This early phase is usually over by the end of the first week but may extend into the second week"(reference 13). What made you choose the ≤6 days as an early-stage criteria , instead of ≤7 days or ≤14 days ?

Response: Thank you for this valuable comment. Contrast-enhanced CT was generally performed approximately 3-10 days after AP onset, with an average of 7 days. Thus, "early stage" in the paper mean that PSMVT occurred within 10 days after AP onset. I apologize for my insufficient explanation. We added more precise information (pages 8, 12).

Comment 3: Variables inclusion criteria: Regression analysis was the major statistical methods in the research. Different variable selection criteria are relevant to the different end results. Can you provide the basis for choosing these variables (showed in Table 2 and Table 3) or the basis for Data collection (Page 9) ?

Response: Thank you for your valuable comment. The study of risk factors for PSMVT has not yet been conclusive. So we included as many relevant factors as possible for univariate analysis (Table 4). Then, we included meaningful indicators into multivariate analysis to find out independent risk factors (Table 5). Table 2 describes imaging data of all patients and Table 3 describes clinical outcomes of all patients to make the paper more complete. Table 1, 2 and 3 were put into supplementary materials to make the paper more concise and focused.

Comment 4: Twenty-five of the 140 (17.86%) SAP patients developed PVT (Page 5 and 13) According to the Atlanta classsification in 2012, SAP include Moderately severe acute pancreatitis and Severe acute pancreatitis. Can you tell me the principal diagnosis of the 140 patients, i.e., it is Moderately SAP and SAP, or SAP only ?

Response: We enrolled patients with SAP only, which was defined according to 2012 Atlanta classification (page 9).

Comment 5: A spelling mistake Page 19: 13 Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis-2012: revision of the Atlanta class sification and definitions by international consensus. Gut 2013; 62: 102-111 [PMID: 23100216 DOI: 10.1136/gutjnl-2012-302779] Pay attention to the word "class sification", there is a space between "class" and "sification" . It is obviously wrong.

Response: I apologize for our mistakes. I revised this.

Comment 6: splenic vein (SpIV) The word "splenic vein " seldom expressed in abbreviations in many paper, especially abbreviated "splenic vein " to "SpIV". Can you provide a basis for this?

Response: Thank you for this comment. The abbreviation was not used in the revised version.

Reviewer 2

The authors report on occurrence of splanchnic venous thrombosis in Acute Pancreatitis through a retrospective study. As such, the literature on occurrence of this complication is well recognised and the study has no apparent novelty.

Comment 1: How were the CTs reviewed. Were those scans or films? How many reviewers?

Response: Thank you for this comment. All contrast-enhanced CT scans were reassessed and reviewed by a radiologist who specialized in abdominal imaging and was blinded to the clinical data (page 8).

Comment 2: Some previous reports have differentiated between splanchnic thrombosis and attenuation of these vessels. Have authors differentiated these two radiological situations

Response: Yes, we had differentiated between splanchnic thrombosis and narrowing of splenic vein. Thrombosis was defined as a filling defect within the lumen of the vessel seen on contrast-enhanced CT images (page 9). Narrowing of splenic vein was defined as >50% decrease in caliber of the lumen (Supplementary Table 2).

Comment 3: One would disagree with the label of gut wall inflammation merely on basis of CT findings; better to report as bowel wall thickening

Response: I apologize for my inaccurate expression. Inflammation in the

gastrointestinal tract (GIT) was defined as the thickening and edema of the GIT wall, with wall thickness greater than 4 mm, and as robust enhancement of the mucosa with reduced enhancement of the submucosa (page 9). "Gastrointestinal wall thickening" was more accurate than "inflammation in the gastrointestinal tract". I changed "inflammation in the gastrointestinal tract" to "gastrointestinal wall thickening" in the revised revison.

Comment 4: Hypoalbuminemia has been reported to predict PSMVT but the ODDs ratio is < 1. OR must be for albumin levels and therefore the ODDS for hypoalbuminemia need to be > 1. Or do the authors wish to state that low albumin levels were protective for PSMVT ? The authors say "In our study, hypoalbuminemia with albumin levels≤25 g/L was a good predictor of PVT, with a very low OR (0.031)." which means low albumin is protective as OR is low

Response: I apologize for the statistical error. Additionally, we once more consulted an statistical expert and revised this. Hypoalbuminemia (serum albumin level<25 g/L) (OR: 32.573; 95% CI: 2.711-391.353; P=0.006) was independent risk factors for PVT developed in patients with SAP (pages 4, 11). In our study, hypoalbuminemia with albumin levels≤25 g/L was a good predictor of PVT, with a very high OR (32.573) (page 13).

Comment 5: The authors could also mention the AUROC for albumin and gut edema in the abstract. Were these factors not analysed further?

Response: Thank you for your comment. These factors were analyzed further (Supplementary Figures 1, 2).

Comment 6: Were outcomes in the two groups similar?

Response: Thank you for your comment. We compared outcomes between two groups, and the results were described (pages 10, 11, Supplementary Tables 1-3).

Comment 7: It is better to use the short form of Portosplenomesenteric vein as PSMVT rather than PVT which can be confused by portal vein thrombosis

Response: Thank you for your advise. We changed "PVT" to "PSMVT" in the revised version.

Comment 8: Pseudoaneurysms are late complications of AP; How do authors explain there presence in early AP?

Response: Thank you for this comment. Our study included all patients who

underwent contrast-enhanced CT within 10 days after AP onset, and did find pseudoaneurysms in two patients (Figure 3). Although, pseudoaneurysms were late complications of AP in most cases, we found that it could also occur in the early stage of AP.

Comment 9: Even though it is a retrospective study, the authors could comment if the protocol to manage PSMVT included anticoagulation or not?

Response: Thank you for the valuable comment. We added a description of anticoagulation therapy (page 8). The aim of the study was to investigate prevalence and risk factors of PSMVT in the early stage of SAP. Anticoagulation therapy was not included in the manage protocol of PSMVT at early stage (within 10 days after AP onset), thus, it could truly reflect the prevalence of PSMVT without the influence of anticoagulation therapy (page 8).

Comment 10: Again, the statement "Correcting hypoalbuminemia during the early stage of AP may help prevent the occurrence of PVT." Is unreferenced and possibly out of the scope of this paper. Better be removed

Response: Thank you for your valuable comment. We added more precise information (page 13). In our study, hypoalbuminemia with albumin levels≤25 g/L was a good predictor of PSMVT, with a very high OR (32.573). Thus, we speculated that correcting hypoalbuminemia during the early stage of AP may help prevent the occurrence of PSMVT, which needed further study.

Comment 11: The authors report "However, our study showed no correlation between coagulative markers and the development of PVT, suggesting that coagulative disturbance may not be a direct cause of PVT, as reported before". Which coagulation markers were tested and if none were tested better to remove this statement.

Response: Thank you for your comment. We added more precise information (page 14). Coagulation tests including platelets, prothrombin time, activated partial thromboplastin time, fibrinogen and D-dimer were tested (Table 1), and they were not independent risk factors in the logistic regression analysis.

Comment 12: What are the numbers in brackets in Table 2

Response: Thank you for your comment. Table 2 describes imaging data of all patients, and the numbers in brackets represent the numbers of patients who did not occur the outcomes in the group, and Table 2 were put into Supplementary Table 2.

Comment 13: How was the amount of ascites calculated in Table 3

Response: Thank you for your comment. The amount of ascites was calculated by calculating the amount of fluid from peritoneal puncture and drainage during admission. This has been added to Supplementary Table 3 in the revised edition.

Comment 14: What are the numbers in brackets in Table 3

Response: Thank you for your comment. Table 3 describes imaging data of all patients, and the numbers in brackets represent the numbers of patients who did not occur the outcomes in the group, and Table 3 were put into Supplementary Table 3.

Reviewer 3

Thank you for giving me an opportunity of the review. My comments are as follows. This is a very interesting paper. However, early PVT in SAP patients was not associated with death.

Comment 1: Please add treatment methods for patients with PVT in this study and describe the significance of treatment for PVT from the results of this study.

Response: Thank you for the valuable comment. We added a description of anticoagulation therapy (page 8). The aim of the study was to investigate prevalence and risk factors of PSMVT in the early stage of SAP. Anticoagulation therapy was not included in the manage protocol of PSMVT at early stage (within 10 days after AP onset), thus, it could truly reflect the prevalence of PSMVT without the influence of anticoagulation therapy (page 8). however, when and whether anticoagulants and other treatments were given 10 days after AP onset depended on the decisions made by the attending doctors. Whether these interventions could have affected the long-term prognosis is unclear. We considered this a limitation of this study, which is discussed in the limitations section (page 14).

Reviewer 4

Comments for Authors Your retrospective cohort study examines intra-abdominal thrombosis in the setting of severe pancreatitis. There have

been a number of studies on this topic in the past, and your findings confirm prior observations.

Comment 1: However, one of the most important issues is a long-term prognosis ie, should you begin anticoagulant therapy. Your study does not address this important issue.

Response: Thank you for this comment. We added a description of anticoagulation therapy (page 8). Anticoagulation therapy was not included in the manage protocol of PSMVT at early stage (within 10 days after AP onset), thus, it could truly reflect the prevalence of PSMVT without the influence of anticoagulation therapy (page 8). however, when and whether anticoagulants and other treatments were given 10 days after AP onset depended on the decisions made by the attending doctors. Whether these interventions could have affected the long-term prognosis is unclear. We considered this a limitation of this study, which is discussed in the limitations section (page 14).

Comment 2: You stated that CT's were generally performed three to seven days after admission. Thus, this study really is a prevalence study that is how many patients develop thrombosis at one point in time. This is therefore not an incidence study meaning patients got multiple CT's and you could look at the incidence long-term. Am I mistaken?

Response: Yes, you are right. Our aims was to investigate incidence and risk factors of PSMVT in the early stage of SAP.

Comment 3: It is not surprising that severe inflammation was associated with thrombosis. It would have been interesting to look at your patients who did not have severe acute pancreatitis to determine how many of them developed any intra-abdominal thrombosis.

Response: Thank for this comment. We also hope for larger, prospective studies on this topic.

Comment 4: Should an arterial aneurysm be included? Or are these venous "aneurysms"?

Response: Thank you for your comment. There were pseudoaneurysms

happened in splenic artery (Figure 3). We not only described PSMVT but also other vascular complications such as pseudoaneurysm, narrowing of splenic vein, splenomegaly, Splenic infarction, etc (Supplementary Table 2).

Comment 5: The images are only fair in quality.

Response: Thank you for this comment. We hope that this study will help.

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

Sincerely,
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