

RE:

Dear Editors, and Reviewers

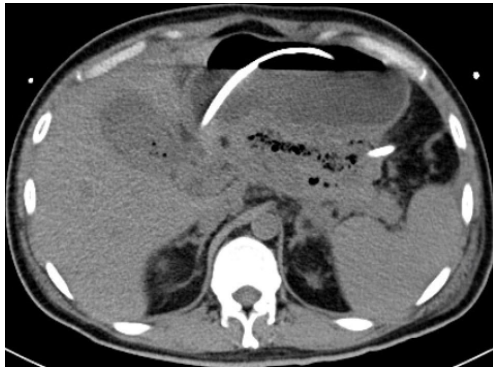
Thank you so much for your time and energy in reviewing this manuscript. We sincerely thank all Editors and Reviewers for their valuable and constructive comments and suggestions, which really helped us in improving this manuscript significantly. We have fully addressed all comments in a point-by-point manner. We appreciate your patience while we made all necessary revisions.

We are submitting a revised manuscript. All authors have read and approved the final revised version. Please refer to the point-to-point response below. We hope the revised manuscript could be more suitable for your consideration of publication in the journal of *World Journal of Clinical Cases*.

Comments by Reviewer 1:

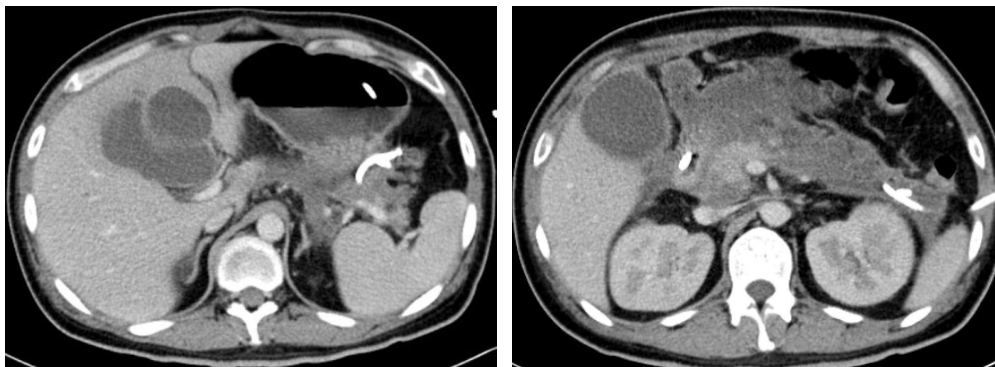
1. Although the authors have shown images, CT and MRI, showing GB perforation (Figure 2), no image showing cholecysto-colic fistula or its findings such as gas in GB lumen or intrahepatic ducts has been included. This could have served as evidence to support the diagnosis.

Reply: Thank you so much for this important suggestion. We have searched for all the CT/MRI images, but unfortunately, we did not identify any images directly demonstrating the cholecysto-colic fistula. We have added Figure 2E for demonstrating gas in the gallbladder lumen before surgery (Line 7/Page 8).



2. The CT images (Fig 1) showing the necrotizing pancreatitis is not demonstrating the GB perforation. Moreover, the images, both CT and MRI, showing the GB perforation (Fig 2) is not demonstrating evidence of pancreatitis. This is because in the figure 2, the authors have intentionally excluded that part of from the figure 2. I am not sure why it is so. It is important that, when possible, both findings be shown in the same image.

Reply: Thanks for your important and constructive comments. We have added Figure 2A and 2C demonstrating gallbladder perforation and pancreatitis one month after SAP onset (Line 22, 24/Page 7).



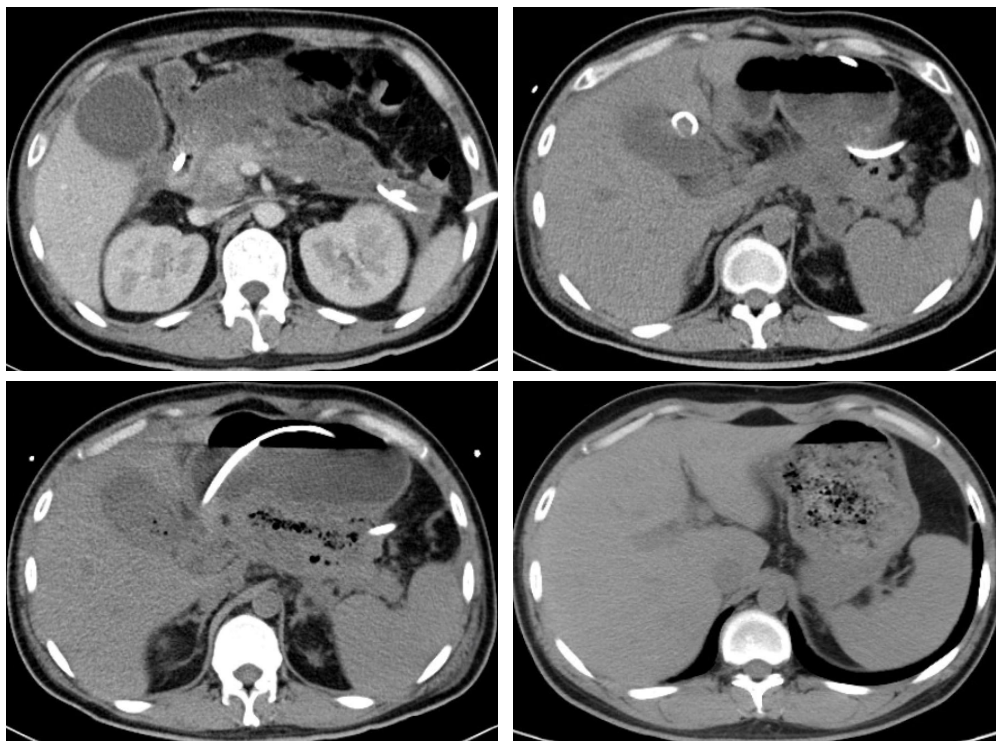
3. In the setting of acute pancreatitis, colonic perforation and gall bladder perforation are two are different entity with different underlying mechanism. While the colonic perforations are common in patients with necrotizing pancreatitis, GB perforation however is rare. But it can occur when distal CBD is obstructed due to pancreatitis, even in absence of calculus. The gall bladder

perforation or the fistula should be highlighted in the report rather the colonic perforation throughout the manuscript, in the introduction, the report and the discussion sections.

Reply: Thanks for your important suggestion.

In the INTRODUCTION, we have added epidemiological data on gallbladder perforation (Line 5-9/Page 5): Gallbladder perforation occurs in 2-10% of patients with acute cholecystitis, usually happens in elderly males, and is mostly associated with calculous cholecystitis. Delay in diagnosis leads to poor prognosis. One study reported that the morbidity and mortality of gallbladder perforation were 37.5% and 12.5%, respectively.

In the REPORT part, we have added Figure 2C to 2F demonstrating changes in the gallbladder during the course of the disease (Line 24-26/Page 7, Line 7, 22/Page 8).



In the DISCUSSION part, we have highlighted gallbladder perforation in the first two paragraphs (Line 2-20/Page 9): Gallbladder perforation could

cause diffuse peritonitis or only localized peritonitis, if wrapped by surrounding tissues, which is commonly seen in calculous cholecystitis and sometimes in cancer or trauma. Acalculous gallbladder perforation in AP, on the other hand, is extremely rare. In this case, gallbladder perforation was diagnosed one month after the onset of SAP, which was confined without causing generalized biliary peritonitis. One possible explanation for gallbladder perforation is that poor bile drainage caused by pancreatic edema and peripancreatic exudation leads to increased pressure in the gallbladder, causing gallbladder wall ischemia and necrosis; fasting after SAP onset and jejunal nutrition further increased the intraluminal pressure of the gallbladder according to animal models. Secondly, pancreatic enzymes of the peripancreatic effusion in the omental sac can erode the gallbladder.

4. Several laboratory parameters are not relevant to this case; they could be omitted. Given that this patient had raised conjugated bilirubin, authors should include the serum alkaline phosphatase level, which can be an important parameter to determine bile duct obstruction.

Reply: Thanks for your important suggestion. We have omitted some parameters as HCT, INR, fibrinogen, D-dimer and ferritin and added alkaline phosphatase level at admission (67 U/L) and when GB perforation occurred (340 U/L) (Line 26/Page 6, Line 20-21/ Page 7).

Comments by Reviewer 2:

1. The authors should tabulate the blood sample test results and show the reference range of each item.

Reply: Thank you so much for your constructive suggestion. We have added Table 1 to demonstrate the basic blood sample test results and show the reference range (Line 26/Page 6).

Table 1 Laboratory examinations at admission

Test item	Test result	Reference range
White blood cell ($\times 10^9/L$)	8.7	3.5 – 9.5
Hemoglobin (g/L)	78	120 – 160
Platelet ($\times 10^9/L$)	206	100 – 350
Alanine aminotransferase (U/L)	230	9 – 50
Alkaline phosphatase (U/L)	67	45 – 125
Total bilirubin ($\mu\text{mol/L}$)	17.1	5.1 – 22.2
Conjugated bilirubin ($\mu\text{mol/L}$)	9.9	0 – 6.8
Potassium (mmol/L)	4.4	3.5 – 5.5
Serum urea (mmol/L)	19	2.78 – 7.14
Serum creatinine ($\mu\text{mol/L}$)	404	59 – 104
Creatine kinase (U/L)	42853	24 – 195
Myoglobin ($\mu\text{g/L}$)	88925	10 – 92
High-sensitivity C-reactive protein (mg/L)	>250	< 3.0
Erythrocyte sedimentation rate (mm/h)	>140	0 – 15
Procalcitonin (ng/ml)	16	< 0.25
Blood cultures	Negative	Negative

2. If available, please provide the intraoperative picture of gallbladder and transverse colon while the surgery of the debridement and ileostomy.

Reply: Thanks for your inspiring comment. The surgical image really helps to understand the clinical manifestations. Unfortunately, we didn't take any

photos in the surgery of the peripancreatic debridement and ileostomy. We apologize for this unintentional fault.

3. The pathological results of gallbladder and transverse colon should be provided.

Reply: Thank you for this important suggestion. Pathology of gallbladder showed chronic inflammation of fibrous connective tissue (Line 22-23/Page 8). Since no obvious abnormality was found under preoperative colonoscopy, we only performed colostomy reduction without sample the transverse colon.

4. The authors should indicate the figure numbers of imaging examinations in the manuscript where they were referred.

Reply: Thank you for this important comment. We have added the figure numbers in the text accordingly (Line 2-3, 16, 22-26/Page 7, Line 2, 7, 11,21-22/Page 8).

5. The authors should provide the time course after the treatment in a brief way, such as when the patient started oral intake, when he was discharged after the surgery, and how long he has been free from the symptoms now.

Reply: Thank you for your constructive suggestion. We have added the time course of this case (Table 2) (Line 26-27/Page 8).

Table 2 Time course of this case

Time	since	SAP	Clinical Events
onset			
11 days			Started jejunal nutrition

1 month	Gallbladder perforation Percutaneous drainage
2 months	Peripancreatic infection Antibiotics and percutaneous drainage
3 months	Cholecysto-colonic fistula and descending colon fistula Peripancreatic debridement and ileostomy
4 months	Normal body temperature Discharged from hospital
6 months	Started oral intake
7 months	All drains removed
10 months	Cholecystectomy and ileostomy reversal
15 months	Free from the symptoms after surgery

6. Please provide the data about his social history such as smoking, drinking, dietary and other risk factors.

Reply: Thank you for your important suggestion. We have added the description of patient's life style (Line 14-15/Page 6): the patient liked fatty food, and smoked 40 cigarettes per day for 10 years and drank 500 ml of liquor per day for 10 years.

All the Above was our point-by-point Reply to All the comments of Reviewers. And we had made all necessary modifications and updating in the revised manuscript (with highlighting marked) meanwhile. These valuable comments and suggestions really helped us to improve our manuscript a great deal.

Hopefully, Editors and Reviewers can review our revised manuscript for further consideration of its acceptance to the journal of *World Journal of Clinical Cases*.

If you have any questions or suggestions, we shall always be happy to address them all and improve the manuscript further.

Best regards for the Chinese Spring Festival,

Yours sincerely,

Qipu Wang, MD