Manuscript ID: 86326

Title: The efficacy and safety of endoscopic retrograde cholangiopancreatography in recurrent pancreatitis of pediatric asparaginase-associated pancreatitis

Point-by-Point Response

Please note that the changes made do not influence the content, conclusions, or framework of the paper. We have not listed below all minor changes made; however, these are highlighted in yellow in the revised manuscript.

Response to Reviewer 1:

1. The sample size of the study is a relatively small.

Response: There are couple reasons for the small sample size in this study. Firstly, in cases of recurrent pancreatitis after AAP, the common approach is to opt for fluid replacement therapy, nutrition, and pain management. The ERCP procedure is technically challenging and not widely performed in most hospitals. Secondly, children with leukemia are a unique patient group. The innovative clinical application of ERCP for treating recurrent pancreatitis in this context is noted. (Page 10–11)

2. Several factors influence the outcome of the study. Please discuss these.

Response: We have added a discussion of the factors that influence the outcome of the study. Due to the underdeveloped nature of the rural area from which the patients originated, access to hospital resources is limited. This limitation could potentially contribute to the onset of pancreatitis, abdominal pain, vomiting, and weight gain among the patients. Furthermore, our study had a relatively short follow-up duration, averaging 1.2 years. This shorter duration may also impact the results of ERCP in AAP. (Page 11)

3. Please review the literature and add more details in the discussion section.

Response: In the discussion section, we have added more details related to the diagnosis and pathophysiology of AAP, and expanded upon the indications for ERCP in children, its procedural aspects, and safety considerations. We have also included information about the occurrence rate of pancreatic pseudocyst in AAP and discussed the limitations of this study. Additionally, we have highlighted the innovative aspects of this study. (Page 8–11)

4. Please add the limitations of the study.

Response: In the discussion section, we have added the limitations of the study. There are several limitations in the present study. First, this was a single-center and retrospective study with potential biases in inclusion criteria. Second, the sample size is notably limited due to the technically demanding and less commonly available nature of the ERCP procedure in most hospitals. The prevalent approach for cases of

recurrent pancreatitis post-AAP prioritizes fluid replacement therapy, nutrition, and pain management. Additionally, it's important to note that ERCP is still in the process of development and refinement, especially concerning its application for children with leukemia. Third, there is no control group in our study. Fourth, due to the underdeveloped nature of the rural area from which the patients originated, access to hospital resources is limited. This limitation could potentially contribute to the onset of pancreatitis, abdominal pain, vomiting, and weight gain among the patients. Finally, our study has a relatively short follow-up duration, averaging 1.2 years. This shorter duration may also impact the results of ERCP in AAP. (Page 10–11)

5. What is the new knowledge of the study.
Response: To our knowledge, the efficacy and safety of ERCP in recurrent pancreatitis of ASP in children has not been reported to date. This study is the largest single-center case report in China, with more details than has been previously reported. (Page 10)

6. “How to apply this knowledge in clinical practice?”.
Response: For AAP complicated by recurrent pancreatitis with pancreatic pseudocyst and pancreatic duct lesions (stones, pancreatic duct stenosis, or dilatation), ERCP intervention appears to be effective and safe. Further, ERCP seems to have a protective effect against pancreatic injury caused by repeated use of ASP. As a consequently, these patients can rapidly resume chemotherapy, which improves their outcome with regarding to the underlying malignant disease. (Page 11)

Response to Reviewer 2:
1. What percentage of patients with asparaginase induced pancreatitis develop recurrent pancreatitis.
Response: Currently, there is limited research on recurrent pancreatitis after ASP, and the occurrence rate is not clear. According to research, up to 63% of children had a second recurrence of pancreatitis. Thus, repeated use of ASP is not typically recommended.

2. Does stopping the use of asparaginase in patients who developed pancreatitis not prevent future attacks of pancreatitis? Or is it so that asparaginase cannot be stopped in pediatric patients with ALL.
Response: If discontinuing ASP, a minority of patients experience repeated pancreatitis, ultimately may lead to chronic pancreatitis. The overall incidence of AAP is 2%–18%, with 7%–66% of cases classified as severe; the mortality rate due to AAP is as high as 2%. If AAP has taken place, repeated use of ASP is not recommended. ASP is the key drug inducing remission and achieving long-term disease-free survival in ALL. Therefore, in our study, we focused on how to prevent relapsing pancreatitis for AAP, with the aim of still being able to use asparaginase even though AAP.

3. Instead of postoperative pancreatitis would be better to use the term 'post ERCP pancreatitis'，
Response: We have revised “postoperative pancreatitis” to “post ERCP

pancreatitis".

4. Does asparaginase induced pancreatic stone development or these patients already had underlying chronic pancreatitis.
Response: Pancreatic duct stones (PDS) are stones formed in the main pancreatic duct and pancreatic duct branches. They are a manifestation of protein embolism or mineralization (caused by calcium carbonate or protein in the pancreas precipitating in the pancreatic ducts) and are characteristic pathological changes of chronic pancreatitis. PDS and pancreatitis are mutually causal. Recurrent pancreatitis leads to increased secretion of pancreatic juice and the activation and concentration of a large amount of trypsinogen in the pancreatic ducts, leading to the formation of pancreatic stones. Pancreatic duct stones block the pancreatic ducts, causing stenosis or dilation of the pancreatic ducts and subsequent recurrent pancreatitis. (Page 9)

5. Was endoscopic cystogastrostomy done for the pancreatic pseudocysts in study patients.
Response: In this study, we did not perform cystogastrostomy through endoscopy. Instead, we employed endoscopy to sphincterotomy, placed a stent, and manipulated a balloon for the treatment of pseudo-cysts.

6. Please mention the mean duration of post-ERCP follow up of the study patients
Response: We have added the mean duration of post-ERCP follow up of the study patients. (Page 6)