Author’s response to reviews

Title: Endoscopic transpapillary drainage in disconnected pancreatic duct syndrome after acute pancreatitis and trauma: Long-term outcomes in 31 patients

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Version: 1 Date: 08 Feb 2019

Author’s response to reviews:

Reply to Editor and Reviewers

Thank you very much for your interest in our manuscript entitled “Endoscopic transpapillary treatment of disconnected pancreatic duct syndrome after acute pancreatitis and trauma: Long-term outcomes of 31 patients”. To aid in the re-review of this manuscript, we have included a point by point response to each comment. In addition, within the revised manuscript, changes to the text in response to the comments are underlined.

We appreciate the suggestions and comments by the editor and the reviewers. As a consequence of these valuable suggestions, we believe that our manuscript has been much strengthened.
Editor Comments:

1) Please remove the sections Competing interests, patient consent, ethics approval, sources of support, acknowledgements, conflicts of interest and author contributions from the title page. The Declarations section should be inserted before the References and contain all sections outlined in our submission guidelines (https://bmcgastroenterol.biomedcentral.com/submission-guidelines/preparing-your-manuscript/research-article#declarations).

Response: We apologize for the poor exhibition. We appreciate the Reviewer’s comments on this. Accordingly, we have removed this section from the title page and inserted this section before the references as suggested, which contained all sections outlined according to the guidelines.

In response to the reviewer’s comment, we have modified the competing interests, patient consent, ethics approval, sources of support, acknowledgements, conflicts of interest and author contributions as follows:

“Ethics approval and consent to participate

The study protocol was approved by the Changhai Hospital Ethics Committee (reference number: CHEC2008-040). All patients provided written informed consent.

Consent for publication

An informed consent was obtained from all the patients prior to procedure.

Availability of data and materials

All data generated during this study are included in this published article. The datasets analysed are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

There are no sources of funding.

Authors' contributions

Yan Chen, Yueping Jiang and Wei Qian participated in the data acquisition, analysis, and interpretation of data, as well as in the manuscript drafting; Qihong Yu, Yuanhang Dong, Huiyun
Zhu, Feng-Liu, Yiqi Du participated in data acquisition and revision of the article for important intellectual content; Dong Wang and Zhaoshen Li contributed to the conception, design, and final approval of the article. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.”

(Line 1, Page 15)

2) Please include the heading Conclusions at the start of this section.

Response: Thank you for your suggestion. In response to the reviewer’s comment, we had added the heading conclusions to the section as follows:

“Endoscopic transpapillary drainage is an effective option for patients with DPDS.”

(Line 1, Page 4)

3) Please list the abbreviations used in the manuscript and include these after the Conclusion section.

Response: We appreciate your suggestion. In response to the reviewer’s comment, we have inserted the list after the conclusion section as suggested:

“List of abbreviations

ANP: acute necrotizing pancreatitis

CT: contrast-enhanced computed tomography

DPDS: Disconnected pancreatic duct syndrome

EPF: external pancreatic fistula

ERCP: endoscopic retrograde cholangiopancreatography

ETD: Endoscopic transpapillary drainage

MPD: main pancreatic duct

MRCP: magnetic resonance cholangiopancreatography

PD: pancreatic ductal
PFC: peripancreatic fluid collections”

(Line 17, Page 14)

4) Do not report p values of 1. Use >0.99 or similar.
Response: Thanks for correcting, we have modified them as suggested (p >0.99).
(Table 1, Table 2, Table 3)

Reviewer reports:

Raj Shah (Reviewer 1):
The authors present a difficult and complex patient population. Efforts to improve outcomes in these patients with DPDS are often extensive with difficult results. However, I am unsure that the authors present a compelling thesis to support the transpapillary stenting technique alone especially if a co-existing PFC is present that even if small can be a window for transmural drainage to provide, indirectly, drainage of the 'disconnected' aspect of the pancreas. See below re: specific suggestions and questions:

1) 31 pt with DPDS. What was the denominator of pts during this time period that had ANP or abd trauma-related pancreatitis to give us an idea of incidence?
Response: Thank you for the thoughtful comments. We treated about 50 cases of ANP every year during this period (2008~2016), the incidence of DPDS with ANP in our center was less than 2%. In this study, all patients with abd trauma-related pancreatitis and most patients with ANP were treated in the local hospital first. After stabilizing the condition, they came to our center for endoscopic treatment of DPDS.

In response to the reviewer’s comment, we have added the sentences to “BACKGROUND “and “METHODS “as follows:

“The incidence of DPDS with ANP in our center was less than 2%.”
“Most of them were treated in local hospitals, they came to our center for endoscopic treatment of this delayed complication when the condition of ANP or abdominal trauma was stable.”

2) What is the baseline average volume of each of the 4 ERCP doctors?
Response: We appreciate the reviewer’s thoughtful comments. During this period, according to the data of ERCP, the mean number of ERCP operations performed by four doctors was 200, 200, 300, and 400 respectively.

3) Were patients from two centers or more?
Response: We appreciate the reviewer’s question. This is a single center study. Most of the patients were transferred from the local hospital to our center for treatment of DPDS.

In response to the reviewer’s comment, we have added the sentences to “METHODS “as follows:

“Most of them were treated in local hospitals, they came to our center for endoscopic treatment of this delayed complication when the condition of ANP or abdominal trauma was stable.”

4) Nearly half of patients had PFC - was transmural drainage considered in those pts and if not why?
Response: We appreciate the reviewer’s insightful comments. Treatment should vary depending on the site and accessibility of the pseudocysts. A case (PFC 11.4cm, this patient required endoscopic ultrasound-guided transmural cystoduodenostomy with placement of a plastic stent and 7 days of hospitalization and recovered 3 months later, line18 page 9) in our study was indeed suitable for transmural drainage. Although we often use transmural drainage currently for pancreatic cysts that are close to the gastric or duodenal wall instead of percutaneous drainage, we may still use transpapillary drainage for DPDS, such as “reference [30] Wang SL, Zhao SB,

In response to the reviewer’s comment, we modified these sentences as follows:

“This study shows that ETD is safe and effective; however, postoperative infection was reported in 1 patient with PFC, which could be initially treated with transmural drainage.”

(line 17, page 13)

5) When you state "The stent was inserted with its proximal end at the site of disruption" was 'disruption' where there was complete cut-off of the duct and/or extravasation of contrast?
Response: Thank you for your suggestion. We apologize for the poor exhibition. “Disruption” means a guidewire could not traverse this disconnection, with nonopacification of the PD upstream from the site of disruption
In response to the reviewer’s comment, we have modified the description as follows:

"The stent was inserted with its proximal end adjacent to or entering disruption”.

(line 12, page 9)

6) Did any stents bridge the level of obstruction?
Response: Thank you very much for your question. There was no stent bridging the obstruction. This content was described in “Technique” section “We attempted to bridge the disruption in all patients, although this was not possible in all” and “Discussion” section “It should be mentioned that it was impossibility to make bridging therapy in all cases in our study with the experienced doctors”.

“Until recently, it has reported a case of successful bridging in our center. 30(line 7, page 13)”. This happened in 2018.
In response to the reviewer’s comment, we have revised the description as follows:

“Up to date, there was only a successful bridging in our center, which was reported in 2018. 30”

(line 9, page 13)

7) Only 55% had clinical success and 8 pts required surgery. I wonder if combining transmural and percutaneous drainage may have improved the clinical success percentage. Please comment on this potential in the discussion.

Response: Thank you for the thoughtful comments. It has been reported that the combination of these two methods can not only accelerate drainage, but also avoid leakage in the treatment of local complications of acute pancreatitis.

In response to the reviewer’s comment, this part has been discussed in “Discussion” section as follows:

“In many of these cases, DPDS was overlooked initially, and the patients were only diagnosed with DPDS once they develop an EPF after percutaneous drainage. In this condition, percutaneous drainage alone should be avoided for patients with DPDS because of the inevitable development of an EPF in these patients. Dual modality drainage is a good treatment option for these patients if the cyst is properly located. It involves the placement of percutaneous drains followed immediately by endoscopically placed transmural stents into the PFC. After transmural drainage is completed, the percutaneous drain is also opened. Once the fluid collection resolves, the percutaneous drain is removed.24”

(line 20, page 11)

References have also been added as follows:


(line 10, page 17)
The order of subsequent references has also changed.

In the future treatment, we will also consider its application if the location of pancreatic cyst is appropriate.

8) Authors bring up an interesting point about atrophy developing in 10 pts. How many of the 10 had PJ surgery? Did these pts have pain resolution?

Response: We appreciate the reviewer’s insightful question. Of these 10 patients, 2 had surgery. The two patients had neither ETD nor sphincterotomy. One had traumatic pancreatitis with pseudocyst (5 cm) underwent pancreatojejunostomy 16 months after ERCP, and the other had ANP with pancreatic fistula underwent pancreatojejunostomy one month after ERCP. Both of them had no recurrence of pancreatic fistula or pseudocyst, but the latter still had abdominal pain accompanied by back radiation pain.

In response to the reviewer’s comment, we have inserted description to discussion as follows:

“Two of the 10 patients with pancreatic atrophy underwent pancreatojejunostomy during follow-up. The two patients had neither ETD nor sphincterotomy. Both of them had no recurrence of pancreatic fistula or pseudocyst after operation, but one patient still had abdominal pain.”

(line 15, page 12)

9) In discussion instead of saying 'proximal' pancreas and 'distal' pancreas, describe anatomical aspects of the pancreas to avoid confusion.

Response: Thank you very much for your suggestion. In response to the reviewer’s comment, we had modified it according to your suggestion:

“DPDS occurred predominantly in the head or neck of pancreas (22/31, 71%) owing to the unique pancreatic anatomy that increases the susceptibility of this region.”

(line 9, page 12)
“This is perhaps because pathology of head/neck duct affects the pancreatic parenchyma to a greater extent than disruptions in the body-tail area, where a small amount of viable pancreatic parenchyma exists upstream to the ductal disruption.”

(line 12, page 12)

Reviewer 2 (Reviewer 2): PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?

Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?

No - there are minor issues

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?

No - there are major issues

Statistics - Is the use of statistics in the manuscript appropriate?

No - there are issues with the statistics in the study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?

No - there are minor issues

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?

Maybe - with major revisions
GENERAL COMMENTS: Overall, the introduction, and study objectives are clear. However, the sample sizes are small, only 31. Several measures of subjects had large variations.

Response: We appreciate the reviewer’s insightful question. This is a preliminary observational research, exploring the feasibility and safety of an endoscopic technology in treating DPDS, a delayed complication of pancreatitis (ANP or trauma related). The minimum follow-up time was 22 months (median 40 months). We found that transpapillary drainage had some effect in treating this syndrome, and recommended that it worth trying before surgery. There are some deficiencies of our research, which have been explained in detail in the discussion section: “Limitations of our study: 1) this was a retrospectively designed study, 2) a small number of cases were included. Because of the low incidence of DPDS, it is difficult to study large patient cohorts. Nevertheless, our sample size is larger than those in previous reports, and notably, the follow-up duration is long enough, 3) a potential selection bias toward endoscopic transpapillary management vs. transmural or surgical management cannot be ignored, which is attributable in part, to our large and experienced ERCP practice and, 4) other drawbacks include that 16.1% of the patients were lost to follow-up.”

Up to date, the number of patients who met the diagnostic criteria of DPDS and were treated with ERCP is less than 31. The table (Response Letter) summarizes the study of DPDS treated with transpapillary drainage. Although there were 167 DPDS in one study, the diagnostic criteria was indistinct. Except this, only 7 patients underwent transpapillary drainage.

In response to the reviewer’s comment, we have modified some explanations in “Discussion” as follows:

“To our knowledge, the number of patients who met the diagnostic criteria of DPDS and were treated with transpapillary drainage was less than 31.1,10,12,13,21,33”

(line 2, page 14)

“2) a small number of cases were included. Because of the low incidence of DPDS, it is difficult to study large patient cohorts. Nevertheless, our sample size is larger than those in previous reports, and notably, the follow-up duration is long enough,”

(line 4, page 14)
Accordingly, an article has also been added to References as follows:


(line 29, page 17)

Thank you again for your recognition and valuable comments. In the future work, systematic reviews and prospective, randomized multicenter trials are needed to make up for these shortcomings.

REQUESTED REVISIONS:

Major reversion is needed (see Summary Comments).

ADDITIONAL REQUESTS/SUGGESTIONS:

Some interpretations are confused or misleading. Such as this sentence: "In our study, patients with acute abdominal trauma were younger than patients with ANP; however, this difference was statistically insignificant (P=0.051)."

Response: Thank you for your suggestion. We apologize for the poor exhibition. We would like to express that there is a younger trend in the trauma group.

In response to the reviewer’s comment, we decided to delete these sentence in the results and discussion section.

“Patients with acute abdominal trauma (median 32 years, range 23–54 years) were younger than patients with ANP (median 42 years, range 25–70 years); however, this difference was statistically insignificant (P=0.051) (Table 1).”

(line 15, page 8)

“In our study, patients with acute abdominal trauma were younger than patients with ANP; however, this difference was statistically insignificant (P=0.051).”
Accordingly, the following sentence was modified as follows:

In our study, the ANP group showed a higher rate of CT-guided percutaneous drainage than the trauma group (P=0.006).

Except these, Reference“12”has also changed its position in the “Discussion” section.