

ROUND 1

23rd January 23, 2021

Dear Editor and Reviewers,

Thank you very much for your time and expertise involved in critically reviewing our submission and for your valuable suggestions.

We have revised our manuscript to address the comments of the editors and reviewers. A detailed point-by-point response is provided below.

We have supplied a clean version of the revised manuscript in Word:

IPMN RAP rev clean and revised tables (Tables 3a, 4a, 5a) and additional figure (Figure 1)

Sincerely yours,

Thiruvengadam Muniraj MD

Editorial Office's Comments:

1. Science editor:

1 Scientific quality: The manuscript describes a retrospective cohort study of the resection of pancreatic cystic neoplasms in patients with recurrent acute pancreatitis prevents recurrent pancreatitis but does not identify more malignancies than in control patients. The topic is within the scope of the WJG. (1) Classification: Grade D, Grade B and Grade C; (2) Summary of the Peer-Review Report: The authors reported an interesting study about recurrent pancreatitis in patients with pancreatic cysts, which is well described. However, the details of surgical intervention should be provided. The questions raised by the reviewers should be answered; and (3) Format: There are 5 tables. A total of 19 references are cited, including 4 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade A, Grade B and Grade B. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, and the Institutional Review Board Approval Form. Written

informed consent was waived. The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. The topic has not previously been published in the WJG. 5 Issues raised: (1) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout; (2) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text; and (3) The reference’s number cited in the text should be superscript. 6 Re-Review: Required. 7 Recommendation: Suggest to transferring WJCC.

Author response:

- Among the 29 patients with RAP with cystic neoplasms, the surgical procedure performed was Whipple surgery (n=18) or distal pancreatectomy (n=11).
- Conflict of Interest Disclosure form and Copy License Agreement submitted
- PubMed numbers and DOI numbers are provided for all references
- All authors listed in the references
- Article Highlights section added at the end of the text
- Reference number now changes as superscript

(2) Editorial office director:

(3) Company editor-in-chief: I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office’s comments and the Criteria for Manuscript Revision by Authors. The title of the manuscript is too long and must be

shortened to meet the requirement of the journal (Title: The title should be no more than 18 words).

Author response:

- *The title of the manuscript is now changed to 18 words*

Reviewer #1: 03358964

Comments to the Author

- How other causes of AP excluded?

Author response:

All the patients had detailed history of alcohol/smoking obtained and had cross-sectional imaging and endoscopic ultrasound to look for gallstone etiology, other structural causes for pancreatitis. Some of the patients had genetic testing done, but this was not done in all the patients.

Comments to the Author

- Definition of AP

Author response:

Definition of AP is now mentioned with the reference the reviewer suggested.

Comments to the Author

- How many patients underwent surgery only for RAP

Author response:

11 patients had surgery only for RAP

Reviewer # 2 : 05429162**Comments to the Author**

Overall, the authors only performed univariate analysis of the possible factors determining recurrent acute pancreatitis. However, the multivariate analysis based on the result from univariate analysis and known risk factors for recurrent acute pancreatitis (RAP) should be performed.

Author response:

Multivariate analysis with logistic regression now performed based on the univariate results. However, the results did not change any of the outcome or conclusions.

Comments to the Author

[Abstract] 1) As the authors described, the primary outcome is the incidence of RAP post-resection. The main result of this study should clearly describe in the conclusion of the abstract.

Author response:

Yes, the incidence of RAP post-resection is mentioned now in the conclusion of the abstract.

Comments to the Author

[Introduction]

1) Page 5; While the term “pseudocyst” is widely used in the clinical setting, this term includes multiple cystic lesions. According to the revision of the Atlanta classification 2012 (Banks et al. Gut. 2013 Jan;62(1):102-11. doi: 10.1136/gutjnl-2012-302779), they stated that the development of a pancreatic pseudocyst is extremely rare in acute pancreatitis. The authors should mention at least about Acute necrotic collection (ANC) and Walled-off necrosis (WON) when they discuss about the pancreatic cysts in the setting of acute pancreatitis.

Author response:

We have now mentioned about pseudocysts/walled off necrosis differentiating from neoplastic cysts in introduction.

Comments to the Author

[Methods]

Page 6; The definition of acute pancreatitis is not clear. Please describe the definition of the acute pancreatitis

Author response:

Definition of AP is mentioned now

Comments to the Author

Page 6; The authors stated that “those who had RAP, defined as 2 or more episodes of acute pancreatitis without an identifiable cause prior to resection”. The definition of the “identifiable cause” is not clear. Please specify what is the “identifiable cause”.

Author response:

To identify the cause for pancreatitis, all the patients had detailed history of alcohol, smoking, medications obtained and had cross-sectional imaging and endoscopic ultrasound to look for gallstone etiology and other structural causes for pancreatitis. Some of the patients had genetic testing done, but this was not done in all the patients.

Comments to the Author

Page 6; There should be references of the definition of recurrent acute pancreatitis which is 2 or more episodes of acute pancreatitis (Testoni et al. World J Gastroenterol. 2014 Dec 7; 20(45): 16891–16901. doi: 10.3748/wjg.v20.i45.16891).

Author response:

Reference cited now

Comments to the Author

Page 6; The imaging used to diagnose is not clear. Please specify the diagnostic modality used to determine the cystic lesions. Also, please mention the diagnosis is double checked.

Author response:

Imaging used are Contrast Enhanced CT (CECT), MRI, and endoscopic ultrasound (EUS).

We have now mentioned that the diagnosis was double checked.

Comments to the Author

Page 6; The preoperative diagnostic criteria of the IPMNs, both branch-duct and main-duct is not clear. Please specify whether the branch-duct and main-duct IPMNs were clinically diagnosed or pathologically proven. It is also important to interpret the result of this study.

Author response:

Pre-operative diagnosis of IPMNs were based on clinical findings from the images obtained

Comments to the Author

Page 6; The pathological differential diagnosis of the subtypes of IPMNs is not clear. Please specify how to distinguish the subtypes of IPMNs (i.e. performing MUC staining or gene sequencing; Patra et al. Clin Transl Gastroenterol. 2017 Apr 6;8(4):e86. doi: 10.1038/ctg.2017.3.; Furukawa et al. Gut. 2011 Apr;60(4):509-16. doi: 10.1136/gut.2010.210567.).

Author response:

On surgically resected specimens MUC staining, histologic examination and gene sequencing were used for pathologic subclassification- both references Patra et al. and Furukawa et al. are cited now

Comments to the Author

[Methods; Statistical analysis] 1) Page 7; The authors stated that "Statistical analysis was performed by using the statistical algorithms in Review Manager 5.3". The software

used for this analysis (it may be Cochrane Review Manager Software 5.3) and its manufacturer should be described.

Author response:

Changes updated mentioning Cochrane Review Manager Software 5.3

Comments to the Author

[Results]

Page 7; If the preoperative diagnosis was made by using radiologic modalities, the final diagnosis may change according to the pathological diagnosis. Please mention about this possibility.

Author response:

Yes, preoperative diagnosis made based on radiologic modalities. This limitation mentioned now.

Comments to the Author

Page 7; Please describe the numbers of macrocystic type serous cystic neoplasms and microcystic type serous cystic neoplasms, as it may contribute having malignant potential (Kimura et al. Pancreas. 2012 Apr;41(3):380-7. doi: 10.1097/MPA.0b013e31822a27db.).

Author response:

Agree with the reviewer on malignant potential may change based on size of cysts in the serous lesions. Unfortunately, we do not have this data.

Comments to the Author

Page 8; The severity of RAP is not clear. Please specify the severity of the RAP(Banks et al. Gut. 2013 Jan;62(1):102-11. doi: 10.1136/gutjnl-2012-302779; Jang et al. J Gastroenterol Hepatol. 2013 Apr;28(4):731-8. doi: 10.1111/jgh.12121.). Comparison of Pre-Resection and Post-Resection Period in the RAP Cohort

Author response:

All the episodes were mild acute pancreatitis and none of the patients in this cohort had severe acute pancreatitis. The references mentioned.

Comments to the Author

Page 8; It is not clear that the reason of surgical intervention. The pancreatitis episodes per patient prior to resection in the RAP cohort was 2.2. This may indicate that the reason for the surgical intervention may not due to the RAP. Comparison of RAP and Control Cohort

Author response:

The indication for surgery was RAP along with cyst characteristics in 11 patients and among all other patients the indication for surgery was based on the cyst morphology.

Comments to the Author

Page 8; According to the table 3, there is a difference of the location (tail: $p=0.02$). Please reconsider the main text.

Author response:

No clear differences were identified between the cohorts in characteristics of the cystic lesions, including in size, or proportion with malignancy except for location in the tail of pancreas where most cyst patient were without RAP.

Comments to the Author

Page 8; According to the table 3, there is a difference of the pathological subtype. There is also statistical difference the numbers of total IPMN patients. This result indicates both cohorts include non-IPMN patients. If the authors would like to perform the statistical analysis about pathological subtype, the different incidence of the BD-, MD-IPMN and non-IPMN should be taken care of. The specific statistical calculation method should be clarified (please reconsider about statistical subpopulation).

Author response:

We thought the study is underpowered to perform meaningful analysis on the subtype and therefore, will certainly consider to do this once we collected larger numbers.

Comments to the Author

Page 8-9; In table 3-5, the multivariate analysis should be performed. Please take care of the multicollinearity.

Author response:

As mentioned above, multivariate logistic regression analysis was performed taking care of multicollinearity, after the reviewer suggestion. However, the results did not change the conclusion.

Table 3a: Multivariable analysis of all patients (n= 172).

	With RAP (n = 29)	Without RAP (n = 143)	
	Odds Ratio	95% CI	P value
Location of cyst			
Head	-		
Neck	1.240013	[0.19933 7.713993]	0.818
Body	1.736854	[0.570778 5.285173]	0.331
Tail	0.686678	[0.155679 3.028833]	0.62
Diffuse	-		
Pathological subtype			
Intestinal			
Gastric	0.059886	[0.013402 0.267608]	<0.001
Pancreatobiliary	0.454606	[0.122387 1.688636]	0.239
Oncocytic	-		
Unknown	0.355592	[0.088518 1.428472]	0.145
Cyst type			
IPMN total	3.462462	[0.782586 15.31927]	0.102
IPMN - BD	1.660612	[0.558816 4.934779]	0.361
IPMN - MD	-		

Table 4a: **Multivariable analysis of patients with IPMN with and without RAP**

	With RAP (n = 29)	Without RAP (n = 143)	
	Odds Ratio	95% CI	P value
Location of cyst			
Head	-	-	
Neck	1.265446	[0.169046 9.472912]	0.819
Body	0.506621	[0.111835 2.295024]	0.378
Tail	0.572817	[0.090659 3.619267]	0.554
Diffuse	-	-	
Pathological subtype			
Intestinal	-	-	
Gastric	0.096091	[0.020977 0.440165]	0.003
Pancreatobiliary	0.773074	[0.199147 3.001027]	0.71
Oncocytic	-		
Unknown	1.034683	[0.214488 4.991279]	0.966
Cyst type			
IPMN total			
IPMN - BD	1.571892	[0.530571 4.65695]	0.414
IPMN - MD	-		

Table 5a: **Multivariable analysis patients with branch-duct IPMN with and without RAP**

	With RAP (n = 29)	Without RAP (n = 143)	
	Odds Ratio	95% CI	P value

Location of cyst			
Head	-	-	
Neck	-	-	
Body	0.61173	[0.059835 6.254136]	0.679
Tail	0.537057	[0.050552 5.705601]	0.606
Diffuse	-	-	
Pathological subtype			
Intestinal	-	-	
Gastric	-	-	
Pancreatobiliary	0.461648	[0.063565 3.352753]	0.445
Oncocytic	-	-	
Unknown	1.458186	[0.15039 14.13861]	0.745

Comments to the Author

Page 11; the authors stated that “We found that episodes of recurrent acute pancreatitis are rare following surgical resection of pancreatic cystic neoplasms, suggesting that the pancreatic cystic neoplasms were indeed the cause of RAP in almost all cases”. Indeed, the article clearly shows the risk reduction of RAP after the pancreatic resection, it seems further investigation with large population prospective study is needed to prove causal relationship between the cause of RAP and pancreatic resection. Please reconsider this sentence.

Author response:

This sentence is changed now per reviewer suggestion

Although, this study clearly shows the risk reduction of RAP after the pancreatic resection, further investigation with large population prospective study is needed to prove causal relationship between the cause of RAP and pancreatic resection.

Comments to the Author

Minor points

[Introduction] 1) Page 5; The authors stated that IPMN are the most common cystic pancreatic tumors. The IPMN is “neoplasm”, as its name suggests, not a tumor (Intra-ductal papillary mucinous tumor, known as “IPMT” was used before the term of IPMN has been developed).

Author response:

Term tumor has been changed to ‘neoplasm’

Comments to the Author

[Methods] 1) Page 6; The definition and numbers of patients in control cohort, experimental cohort both with IPMN and without IPMN is not clear. Please make a figure to explain entire cohort. Especially, the definition of control cohort is not clear. Please clarify whether the patients with resection who did not have prior RAP but have pancreatic cyst (or cystic neoplasm) served as control cohort.

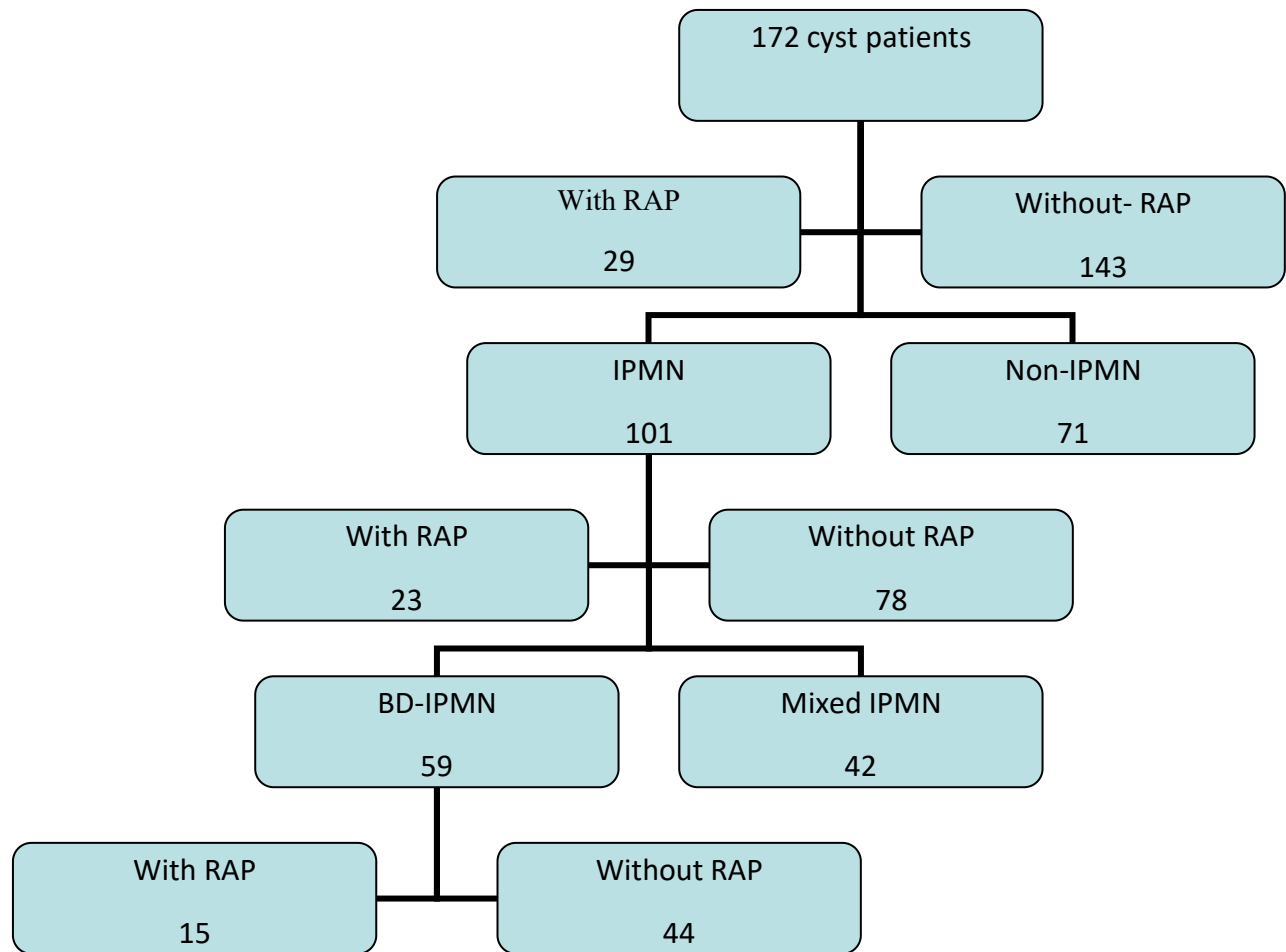
Author response:

Control cohort was patients who did not have RAP.

Yes, patients who did not have RAP but had resection served as controls.

Figure 1 made per reviewer suggestion

- Total cyst patients who had resection: 172 (IPMN- 101, non-IPMN 71)
- Among IPMN 101 – 59 BD and 42 mixed
- Table 3 is for all 172 cyst patients
- Table 4 is for 101 IPMN
- Table 5 is for 59 BD alone



Comments to the Author

Result] Comparison of RAP and Control Cohort 1) Page 8-9; In the table 3-5, not only showing the median age but also the IQR (interquartile range) of age in each cohort should be described. 2) Page 8-9; In the table 3-5; the median cyst size with IQR should be described, as it may affect to the malignant potential (Sadakari et al. Pancreas. 2010 Mar;39(2):232-6. doi: 10.1097/MPA.0b013e3181bab60e). 3) Page 8-9; In the table 3-5, the number of IPMN patients with worrisome features and high-risk stigmata should be described.

Author response:

As different criteria are being used by various centers on classifying the worrisome features and high-risk stigmata, this information was not included in the table.

Size is still a controversial criterion- Kaimakliotis P, Riff B, Pourmand K, Chandrasekhara V, Furth EE, Siegelman ES, Drebin J, Vollmer CM, Kochman ML,

Ginsberg GG, Ahmad NA. Sendai and Fukuoka Consensus Guidelines Identify Advanced Neoplasia in Patients With Suspected Mucinous Cystic Neoplasms of the Pancreas. Clin Gastroenterol Hepatol. 2015 Oct;13(10):1808-15. doi: 10.1016/j.cgh.2015.03.017. Epub 2015 Mar 25. PMID: 25818077.

Reviewer #3:02591964

Comments to Authors: This retrospective study reports an expected outcome. Details of surgical intervention are not provided. Was chronic pancreatitis also ruled out on histopathological examinations. How many patients underwent surgery only for RAP.

Author response:

11 patients underwent surgery for RAP only

Chronic pancreatitis was ruled out on the histopathological exam

Surgery was based on the location of the cyst, Whipple, distal pancreatectomy were two surgeries performed. Details provided now.

Reviewer #4:03883464

I would like to congratulate the authors for this interesting paper. There are a few suggestions and a few questions that I would request the authors to clarify:
Introduction

1. Page 5 line 91- I would suggest authors to include in introduction that the presence of a pancreatic cyst in imaging at diagnosis of pancreatitis is probably the cause of pancreatitis, while the detection of a cyst in the follow-up of pancreatitis with a normal first imaging exam.

This is added in the introduction.

Methods 2. Were all cysts resected or there were surgeries without resection where preoperative classification using imaging and FNA was used? Please clarify in how many patients classification was based on pathology specimens.

All cysts were resected. All post-resections patient's classification was based on pathology specimens.

3. Please specify what where the criteria evaluated to exclude other identifiable causes of recurrent acute pancreatitis besides cystic lesions.

This is now explained under 'Materials and Methods'

4. Please specify follow-time after surgery (mean value, and interval of follow-up).
Discussion

The mean follow-up after surgery was 7.2 years (range 1.9-13.8 years)

5. Please further discuss that, although there is no global increase in malignancy in RAP cysts, malignancy risk is increased in branch-duct IPMNs (n=59). Please further explore by multivariate analysis if it is related to pathological subtype of intestinal type?

Our sample size not powered enough to explore this question. But thank you for this interesting question, we will consider in this for a future study.

6. Please discuss possible reasons why bd-IPMNs have higher risk of RAP than md-IPMNs in this series? Is it related to histological type (bd-IPMNs are predominantly intestinal type in this series). What is the case for md-IPMNs in this series? In the literature md-IPMNs are predominantly of intestinal type. Thank you for the opportunity to review this article.

We have explained this now in discussion on how BD-IPMN causes RAP. But our sample size is not powered enough to explore on why this has more RAP than MD-IPMN. But thank you for this excellent question, we will consider in this for a future study.

ROUND 2

February 28th 2021

Dear Editor and Reviewers,

Thank you very much for your time and expertise involved in critically reviewing our submission and for your valuable suggestions on the 2nd review.

We have revised our manuscript to address the comments of the editors and reviewers.

A detailed point-by-point response is provided below.

We have supplied a clean version of the revised manuscript in Word:

IPMN RAP rev clean_V2 and a revised table (Tables 1)

Sincerely yours,

Thiruvengadam Muniraj MD

Editorial Office's Comments:

2. Science editor:

1. *There are some specific comments to be modified in the second-round review. At the same time, please reply to the reviewer's comments one by one.*

All comments are addressed now with point-by-point responses

2. *The copyright agreement does not meet the requirements and requires autographing by all authors in order.*

All authors have autographed now in the copyright agreement

3. *The STROBE Statement – checklist of items that should be included in reports of observational studies, Please add a page number after each item.*

STROBE statement with page number included

Reviewer #1: Reviewer's code: 02591964

Comments to the Author

1. Page 6, lines 113-116. Introduction: "We therefore performed a retrospective study to assess the characteristics of patients with IPMN who present with unexplained RAP and the effect of surgical resection on the natural history. " However, the study has included other cystic neoplasms as well in the analysis. Aim needs to be modified in view of this and the title of the paper.

Author response:

Agreed and aims is now modified per reviewer's suggestion

Reviewer # 2: 05429162

1. Comments to the Author

Please describe the surgical outcome and complications by surgical procedures. The pancreaticoduodenectomy ("Whipple procedure") has a high mortality and complication rate. It may affect the patients outcome (Paolini et al. Surg Oncol. 2021 Jan 5;37:101515. doi: 10.1016/j.suronc.2020.12.009.)

Author response:

The surgical outcome and complications data given.

Among the 29 patients with RAP with cystic neoplasms, the surgical procedure performed was pancreaticoduodenectomy (n=18) or distal pancreatectomy (n=11). with surgical mortality 0%, morbidity 3/29 (10%) (one patient had mesenteric bleeding requiring immediate exploratory laparotomy, one had afferent limb syndrome 2 weeks later required exploratory laparotomy for adhesion lysis, and other with a delayed abscess in LUQ managed with external drainage,

Comments to the Author

2) The term "Whipple surgery" is not a standard term both in Asia and Europe. The term "pancreaticoduodenectomy" or "pancreatoduodenectomy" is more appropriate

Author response:

Term changed to pancreaticoduodenectomy

Comments to the Author

In table 1, please consider to add the following variables in entire cohort; • Age • Sex ratio

- Location of cyst • Frequency of worrisome features, high-risk stigmata and malignancies*
- IPMN's pathological subtypes*

Author response:

We have now mentioned those variables for the entire cohort, under Table 2

Comments to the Author

In the discussion section, the authors stated that the RAP was more often associated with BD-IPMN. As the authors described, there is a discrepancy from prior report. Please discuss this difference

Author response:

BD-IPMN RAP discrepancy now discussed under discussion.

Comments to the Author

In the discussion section, the authors stated that “We found that episodes of recurrent acute pancreatitis are rare following surgical resection of pancreatic cystic neoplasms, suggesting that the pancreatic cystic neoplasms were indeed the cause of RAP in almost all cases”. I think the sentence is over-interrupted. As pancreatic exocrine function decreases after the pancreas resection (Moore et al. J Gastrointest Surg. 2021 Jan 22. doi: 10.1007/s11605-020-04883-1.), the pancreatic resection itself may decrease the frequency of RAP.

Author response:

Agree, we have now added this in our discussion citing the reference provided by the esteemed reviewer.