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Re: Manuscript 32001 "Assessment of the July Effect in Post-ERCP Pancreatitis: Nationwide Inpatient Sample"

Dear Dr. Gong,

We appreciate the valuable feedback and comments from the editorial staff and reviewers. We have incorporated all of your suggestions into a revised manuscript for your evaluation. We are also including a point-to-point response/summary of the changes that the reviewers requested and including it below.

**Reviewer's code:** 00068723

## COMMENTS TO AUTHORS

The authors investigated seasonal change of incidence of post-ERCP pancreatitis. The aim of this study was the affect of trainee to post-ERCP pancreatitis. There was no difference of incidence of post-ERCP pancreatitis according to early or late of the year. The aim was clear, and the results were useful. It was assumed that trainee did not affect the incidence as the authors stated. Incidence of complication possibly depended on the procedure. Were there any data available the ERCP was stratified to procedure? For example, with or without sphincterotomy, with or without cannulation to pancreatic duct, etc. If not, how did the authors speculate this point? Median income and primary insurance were interesting. Please explain the reason why the authors focused these factors. Was there possibility that incidence of post-ERCP pancreatitis was too low to be statistically significant?

**These are all very interesting questions. Unfortunately, as the National Inpatient Sample (NIS)**

is based on ICD-9 codes, we were unable to stratify the incidence of post-ERCP pancreatitis by whether the patient had a sphincterotomy or cannulation of the pancreatic duct, as neither of these two techniques have an associated ICD-9 code. While this is a limitation to our analysis, we were interested in seeing if rates of post-ERCP pancreatitis varied throughout the academic year, independent of technique.

To address your point, we have added the following statement to the Discussion section:

“Fifth, while these results are compelling given the number of patients included in this database, we are unable to assess whether differences in technique affected PEP rates in this study. The NIS database does not allow the ability to control for factors that may affect the incidence of PEP but do not have a discrete ICD-9 code including inadvertent cannulation of the pancreatic duct, time until successful cannulation, use of sphincterotomy, degree of supervision by attending physician, and so on. Additionally, the database does not reveal the number of ERCPs performed for biliary versus pancreatic indications.

Median income and primary insurance were included in the analysis to control for these factors while calculating adjusted odds ratios through multivariate regression analyses. This is because patient’s socioeconomic status and patient insurance have been previously demonstrated to impact patient’s outcomes in various clinical conditions. We provide few examples of the many reports in the literature about this association: insurance was found to affect outcome for thoracic aortic aneurysm treatment (1), cervical cancer treatment (2) and acute myoblastic leukemia treatment (3). Socioeconomic status was found to affect outcome in atherosclerosis treatment(4), colorectal cancer treatment (5) and total hip replacement treatment (6).

With negative results, there is always a possibility for a beta error, which is the failure to detect a difference between two groups when in fact there is one. However, we have used the largest publically available database in the United States, which contains about 8 million patients and is nationally representative. The risk of a beta error with such large numbers is minimized.

- (1) Murphy EH, Stanley GA, Arko MZ et al. Effect of ethnicity and insurance type on the outcome of open thoracic aortic aneurysm repair. *Ann Vasc Surg.* 2013;27 (6):699-707.
- (2) Churilla T, Egleston B, Dong Y et al. Disparities in the management and outcome of cervical cancer in the United States according to health insurance status. *Gynecol Oncol.* 2016;141(3):516-23
- (3)Pulte D, Castro FA, Brenner H et al. *Outcome disparities by insurance type for patients with acute myeloblastic leukemia.* Leuk Res. 2017 3;56:75-81.
- (4) Shea S, Lima J, Diez-Roux A et al. *Socioeconomic Status and Poor Health Outcome at 10 Years of Follow-Up in the Multi-Ethnic Study of Atherosclerosis.* PLoS One. 2016;11(11):e0165651.
- (5) Aarts MJ<sup>1</sup>, Lemmens VE, Louwman MW et al. Socioeconomic status and changing inequalities

in colorectal cancer? A review of the associations with risk, treatment and outcome. Eur J Cancer. 2010;46(15):2681-95.

(6) Clement ND<sup>1</sup>, Muzammil A, Macdonald D. Socioeconomic status affects the early outcome of total hip replacement. J Bone Joint Surg Br. 2011 Apr;93(4):464-9

**Reviewer's code:** 03648085

#### **COMMENTS TO AUTHORS**

No

Thank you

**Reviewer's code:** 03025323

#### **COMMENTS TO AUTHORS**

This article is mentioned about difference in the incidence of PEP at academic institutions in the early versus the late academic year. I think that this paper is very interesting, because PEP is the most serious complication of ERCP, and we want to know whether the existence of the trainee effects this complication. But I think there are some problems. I would like to know the first operator of ERCP. If the first operator is trainer in the early academic year and is trainee in the late, I am easy to understand these results. I also would like to know how the teaching method is, though I think that it is difficult to know it because of retrospective cohort study. I would like to know the results in the middle academic year, too. The incidence of PEP may be the most high in this time possibly.

**Thank you for these comments and interesting speculations. Given the limitations of using a Nationwide Inpatient Sample, we unfortunately are unable to determine who the first operator is at a given time, but we expect by August that the fellow is doing cases, which is why August and September are included in the analysis to capture the early learning curve. Following this input from the reviewer, we included this possibility in our Discussion section as follows:**

"Fifth, while these results are compelling given the number of patients included in this database, we are unable to assess whether differences in technique affected PEP rates in this study. The NIS database does not allow the ability to control for factors that may affect the incidence of PEP but do not have a discrete ICD-9 code including inadvertent cannulation of the pancreatic duct, time until successful cannulation, use of sphincterotomy, degree of supervision by attending physician, and so on. Additionally, the database does not reveal the number of ERCPs performed for biliary versus pancreatic indications."

**We also ran this analysis on October/November/December/January/February/March and the incidence of PEP in the middle of the year was not statistically different from the incidence in the**

beginning or end of year.

**Reviewer's code:** 01804189

### **COMMENTS TO AUTHORS**

There is no doubt that trainee has less skill and confidence to do ERCP as compared to an expert. It is the supervision by the expert who prevents him committing the mistakes. Since this study is retrospective it is not possible to know to what extent the trainees were allowed to proceed. If a trainee is allowed for long time where he repeatedly tries to manipulate ampulla he will definitely land up in complications. It is not known in the whole study that to what extent the trainees were allowed to proceed. Whether any step wise program was followed where trainees were allowed for eg side viewing endoscopy for a particular time, cannulation for a particular time, intervening if more than four attempts at cannulation, allowing sphincterotomy after a particular no of successful cannulation etc, etc. is not clear from the study. It is a wrong message that ERCP by beginners is safe unless authors outline and give a detail guideline of the level of supervision. Authors should outline the various steps taken by supervisors to prevent complications. It is the person who is properly supervising the ERCP is responsible for less complications rather than the trainee himself.

**Thank you for your review of our article. The results of this study are no doubt to very close supervision being provided in current training programs. There is great concern for patients who require hospitalization or procedures early in the academic year for a variety of conditions. This study shows that our current method of training allows the safe development of ERCP skills in a clinical setting with close supervision from expert endoscopists.**

**We will mention the importance of close supervision and its likely impact on the results of this study in the discussion section:**

**"To clarify, these results do not suggest that novice endoscopists can safely perform ERCP in an unsupervised setting. However, the results of this study show that our current training method allows for the safe development of ERCP skills in a clinical setting, with close supervision from expert endoscopists."**

**Reviewer's code:** 03475360

### **COMMENTS TO AUTHORS**

The article concerns the occurrence of complications after endoscopic retrograde cholangiopancreatography (ERCP) mostly of post-ERCP pancreatitis over the academic year. The similar papers concerning the complications in course of academic year are available in the literature

for various therapeutic procedures. To the best of my knowledge it is the first in the world article concerning therapeutic endoscopy. In my opinion the aims of study are clear, the results and discussion are correct. I find this paper in terms of content suitable for publication in World Journal of Gastroenterology. However, some minor language errors must be fixed. Furthermore, I would like to know how teaching process looks in the involved institutions like. Also, I find the profile and difficulty level of ERCP procedures (biliary or pancreatic etc.) worth to be emphasized in the paper.

**Thank you very much for these remarks. Unfortunately, given that the study utilizes the nationwide inpatient sample (NIS) database and therefore the data is based on ICD-9 codes, we are unable to comment on the percentage of these procedures which were biliary versus pancreatic, as those do not have separate codes. However, this is a great point, and we have added the following statement to the discussion section:**

**"Fifth, while these results are compelling given the number of patients included in this database, we are unable to assess whether differences in technique affected PEP rates in this study. The NIS database does not allow the ability to control for factors that may affect the incidence of PEP but do not have a discrete ICD-9 code including inadvertent cannulation of the pancreatic duct, time until successful cannulation, use of sphincterotomy, degree of supervision by attending physician, and so on. Additionally, the database does not reveal the number of ERCPs performed for biliary versus pancreatic indications."**