המרכז הרפואי ת"א ע"ש סוראסקי

המכון למחלות דרכי העיכול והכבד
Department of Gastroenterology and Hepatology

August 16, 2020

Dear Lian-Sheng Ma,

Company Editor-in-Chief, Editorial Office

World Journal of Gastroenterology

Manuscript NO: 57608

Title: Older Age, Longer Procedures and Tandem Endoscopic-Ultrasound as Risk Factors for Post-ERCP Bacteremia

We would like to thank the reviewers for their comments. We have found their comments constructive and corrected the manuscript accordingly. Please find below our detailed response in a point by point fashion. All changes in the manuscript are highlighted in yellow. We hope that the revisions in the manuscript and our accompanying responses will be to your satisfaction.

Yours sincerely,

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Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: Minor comments: 1. The patients with acute cholangitis before ERCP should be excluded. 2. Blood routine and biochemistry should be evaluated

Response to reviewer #1:

1. **Comment**: The patients with acute cholangitis before ERCP should be excluded

   Response: Thank you for the comment. Patient with acute cholangitis before ERCP were indeed excluded under exclusion criteria c ("scheduled antibiotic treatment prior to ERCP"), since all these patients were administered antibiotic treatment. It is important to mention that all patients with positive blood culture prior to ERCP were excluded as well.
2. **Comment**: Blood routine and biochemistry should be evaluated

   Response: We thank the reviewer for this important comment. We reviewed the charts of all participants and extracted the requested data. Due to the retrospective nature of the study, not all data was available and we explained this in the text. We added the available data as a supplementary table. Because the data was incomplete it could not be entered into the statistical models.

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Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

Specific Comments to Authors: Dear authors In this paper the authors demonstrated in a large retrospective cohort how some factors influence the outcome of ercp, and in particular the incidence of bacteremia and therefore of sepsis. In particular, advanced age, the tandem use of eus and ercp and the long duration of ercp are related to an increased incidence of bacteriemia. First of all although the clinical impact of these results is significant, in the literature there are many studies that analyze these points and therefore the results that emerged are not so original. Secondly, this study highlights how the attitude towards the use of antibiotics is still very heterogeneous and sometimes based to operator's discretion. I would have some major comments: 1. were the tests performed by the same operator? with what experience? have different operators had different outcomes? 2. co-morbidities were not considered in patient selection. It has been shown that these, particularly cirrhosis, have a role in 3. post procedural infections and can therefore influence the outcome. I suggest to take them into consideration and investigate how they affect the incidence of post procedural bacteremia 3. The prophylactic use of pancreatic stents and nasobiliary tubes has not been documented. It has been shown that both positively influence the incidence of post-ercp infectious complications. If data are available, they should be evaluated. 4. The same for laboratory tests: pre-procedural leukocytosis and albumin levels seem to be correlated with the outcome 5. On the basis of these comments references list should be updated Finally I would have one minor comment on the flow-chart: 1. in the last line the sum of the patients (65 and 33) is not 84 as is in the previous line. Please correct and modify if needed.

Response to reviewer #2:

1. **Comment**: were the tests performed by the same operator? with what experience? have different operators had different outcomes?
   Response: All 630 ERCPs were performed by one of five certified gastroenterologists with more than 5-years' experience in advanced endoscopy. In two cases (0.4%) the name of the endoscopist was not documented. There was no difference in the distribution of ERCPs among operators between the PEB and Non-PEB groups. Comments were added to the text in the methods and results sections as appropriate, marked in yellow.
2. **Comment**: co-morbidities were not considered in patient selection. It has been shown that these, particularly cirrhosis, have a role in post procedural infections and can therefore influence the outcome. I suggest to take them into consideration and investigate how they affect the incidence of post procedural bacteremia.
   Response: Thank you for the comment. Co-morbidities are indeed important in patient selection, especially medical conditions in which complete biliary drainage is not likely to be achieved. All relevant conditions were documented in table 1: all patients post-liver transplantation; all abdominal malignancies according to cancer type (pancreas, cholangiocarcinoma, liver metastases and others) and all various indications for ERCP (choledocholithiasis, chronic pancreatitis, obstructive malignancy, benign bile duct stricture (including PSC), elective stent replacement and post-surgical complications).
3. **Comment**: The prophylactic use of pancreatic stents and naso-biliary tubes has not been documented. It has been shown that both positively influence the incidence of post-ercp infectious complications. If data are available, they should be evaluated.

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Response: Thank you for this valuable comment. There was no difference in the prevalence of pancreatic stents utilization among PEB and non-PEB groups. Data was added to the result section and table 1 marked in yellow. Unfortunately, we don't have the data regarding naso-biliary tubes; however they are seldom if ever used in our institute (a sentence stating this was added to the results section marked in yellow).

4. **Comment**: The same for laboratory tests: pre-procedural leukocytosis and albumin levels seem to be correlated with the outcome

   Response: see our comment to reviewer 1 (comment number 2). We added available date in a supplementary table.

5. **Comment**: On the basis of these comments references list should be updated

   Response: We thank the reviewer for the comment. We performed an exhaustive literature review, no recent relevant references were found, and thus, no new refences were added.

6. **Comment**: one minor comment on the flow-chart: 1. in the last line the sum of the patients (65 and 33) is not 84 as is in the previous line. Please correct and modify if needed.

   Response: We regret this unfortunate typo – the number was changed to 61 and the percent to 9.7%.

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