March 12, 2019

Dear Editor:

Title: Causes associated with recurrent choledocholithiasis following therapeutic endoscopic retrograde cholangiopancreatography: a large sample sized retrospective study

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The manuscript has been improved according to the suggestions of the reviewers:
1 Format has been updated
2 Revisions have been made according to the suggestions of the reviewers

Reviewer 1
A quite interesting and easy to follow study from the beginning to the end. Unfortunately the most of the results are well known and reported in previous publishes. The study has all the problems from a retrospective single center study but some comments comes here.

Comment 1: Are there any comments about the treatment method or strategy between patients with second and several instance recurrence. Any strategy?? Why the second category twice as bigger??

Response: Thank you for your comment. ERCP should be done again to clear stones for patients with second and several instance recurrence. In our studies, once choledocholithiasis recurred, the next recurrence rate increased in proportion to the number of instances of recurrence, as reported previously[1,10]. Why the second category twice as bigger is a interesting question, which should be studied in future.

Comment 2: In the core tips side the second sentence begins with wrong size.

Response: Thank you for your valuable comment. I apologize for our mistakes. I revised this.

Comment 3: Figure 1, Kaplan Meijer should absolutely presents in a bigger size so it is possible to follow the events.

Response: Thank you for your valuable comment. I revised Figure 1.

Reviewer 2

The authors should be congratulated on their extensive retrospective review on the recurrence of choledocholithiasis after therapeutic ERCP. Despite their incidence in many experienced centers, the causes for recurrent CBD stones are not completely understood yet. The pathophysiology of every independent risk factor of recurrence of choledocholithiasis has been exhaustively described and the results agree with the mentioned studies. Major remarks

Methods and study design

Comment 1: The original group of patients of the cohort who underwent ERCP is not described (number of patients, age range, demographics, patients who were excluded from the analysis, etc).

Response: Thank you for this comment. The ERCP database of our medical center for the period between January 2007 and January 2016 was retrospectively reviewed, and information regarding eligible patients who had choledocholithiasis recurrence was collected. A 1:1 case control study was used for this investigation. The demographics of patients enrolled were described in Table 1.

Comment 2: Timing of control for recurrence of choledocholithiasis has not been specified. In particular, it is not clear if every patient enrolled had imaging exam after a specific period post-therapeutic ERCP or if imaging exams have been done only after the appearance of new symptoms. In the latter event, a description of symptoms or/and laboratory findings that you decide to consider related to recurrence of choledocholithiasis should be described.

Response: Yes. The choledocholithiasis recurrence was suspected when the symptoms of fever, abdominal pain, jaundice, or other typical symptoms recurred, and was confirmed by abdominal B-scan ultrasonography, computed tomography (CT), or magnetic resonance cholangiopancreatography (MRCP) 6 months after the stones were

completely removed. A description of symptoms or/and laboratory findings that I decide to consider related to recurrence of choledocholithiasis was described in the part of outcome measurements.

Comment 3: It has not been specified if patients without symptoms but with casual finding on laboratory text of cholestasis (and then confirmed by imaging) were enrolled.

Response: I apologize for my inaccurate expression. Patients with the symptoms of fever, abdominal pain, jaundice, or other typical symptoms, and then choledocholithiasis was confirmed by imaging were enrolled. The patients without symptoms but with casual finding on laboratory text of cholestasis (and then confirmed by imaging) were not enrolled. I changed "The patients who revisited our hospital underwent abdominal CT and ERCP to confirm choledocholithiasis" to " The patients with the symptoms of fever, abdominal pain, jaundice, or other typical symptoms who revisited our hospital underwent abdominal CT and ERCP to confirm choledocholithiasis" in the revised revison.

Comment 4: It seems that endoscopic ultrasound was not adopted prior to ERCP. Please explain the reasons.

Response: Thank you for your comment. Choledocholithiasis was confirmed by abdominal B-scan ultrasonography, computed tomography (CT), or magnetic resonance cholangiopancreatography (MRCP). We did not adopt endoscopic ultrasound prior to ERCP.

Comment 5: How was the control group selected?

Response: Thank you for your comment. A 1:1 case control study was used for this investigation.

Results and discussion

Comment 1: Median age-range for case and control group is not calculated. This data should be useful for both the interpretation of results and the study design.

Response: Thank you for your comment. The average age of all patients was 57.43±14.92 years. The average age of recurrence group was 59.74±14.14 years, and the average age of recurrence group was 55.14±15.27 years.

Comment 2: Age greater than 65 years was found to be an independent risk factor for the development of recurrent choledocholithiasis after ERCP; I think that is useful for the interpretation of this results reporting in your tables the median age of case and control group and the age distribution in the entire cohort.

Response: Thank you for your comment.

Comment 3: In table 1, in consideration of your results, maybe you should divide your group with the cut-off of 65 years (for example: <55, 55-65, 65-75, >75) and for every group report the number of patients included.

Response: Thank you for your comment. The age was divided into <50, 50-59, 60-69 and ≥70 years in the Kaplan-Meier analysis, which showed that as age increased, the rate of choledocholithiasis recurrence increased proportionally (Figure 1).

Comment 4: Please add a consideration that the greatest number of independent risk factors for choledocholithiasis recurrence is associated to ERCP-related factors and how, except for age, general patient characteristics are not related to recurrence.

Response: Thank you for your comment. We added it in the revised paper.

Comment 5: Considerations about how past medical history, except for medical history related to biliary system such as cholecystectomy and CBD incision, and laboratory tests (ALT, AST, GGT, cholesterol, triglycerides, ..) are not related to recurrence, should also be added.

Response: Thank you for your comment. We added it in the revised paper.

Comment 6: Introduction: please rephrase and clarify "choledocholithiasis is associated with bacteria, an abnormal biliary structure"

Response: Thank you for your comment. We changed "Many studies have reported that choledocholithiasis is associated with bacteria, an abnormal biliary structure, inflammation, endoscopic and surgical treatment, and other factors" to "Many studies have reported that choledocholithiasis is associated with the infection of bacteria, an abnormal biliary structure, inflammation, endoscopic and surgical treatment, and other factors".

Comment 7: Materials/Patients: please rephrase "patients with stones that could not be removed during the first surgery"

Response: Thank you for your comment. We changed " patients with stones that could not be removed during the first surgery" to "patients were confirmed not to have had their stones completely removed after first choledocholithiasis removal by ERCP".

Comment 8: Results/univariate: please rephrase and clarify "CBD incision"

Response: Thank you for your comment. We changed "CBD incision" to "choledocholithotomy".

Reviewer 3

This paper is well written. Author's idea is very interesting, but results are not so useful and not new. So, author has to collect more data and analyze again. Especially, patient's back ground. Patient's preference, customs, habits, food, hyperlipidaemia and so on.

Response: Thank for this comment. We also hope for larger, prospective studies on this topic.

Thank you again for publishing our manuscript in the *World Journal of Clinical Cases*.

Sincerely,

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