

[在此鍵入]

[06/09/2020]

To the editor,

World Journal of Gastroenterology

Re: Predicting cholecystocholedochal fistulas in patients with Mirizzi syndrome
undergoing endoscopic retrograde cholangiopancreatography

Please find attached, the revised manuscript and the answers to the reviewers' comments below. We would like to thank you and the reviewers for evaluating our manuscript as well as for your time and patience. We have carefully read all comments and suggestions and have revised the manuscript accordingly. The constructive suggestions provided to us have helped improve both the quality and clarity of the manuscript. We hope that the revised paper is now acceptable for publication in the *World Journal of Gastroenterology*. Please let us know if there are any further questions.

Regards,

Yi-Yin Jan, MD

Answering Reviewers:

We are thankful for the reviewer's valuable comments. The manuscript has been edited in response to the reviewer's comments.

Reviewer #1 ID:00001114

Thank you for your kind recommendations.

Major:

#1. The authors concluded that preoperative ERCP findings might aid the diagnosis of Mirizzi syndrome with cholecystocholedochal fistulas. So, the authors should show how

[在此鍵入]

many patients could identify cholecystocholedochal fistulas by preoperative ERCP to evaluate the advantage of the study results. Erben et al. (J Am Coll Surg. 2011 Jul;213(1):114-9) and Tan et al. (ANZ J Surg. 2004 Oct;74(10):833-7.) reported that ERCP was useful to identify cholecystocholedochal fistulas but failed to pick up the syndrome in half of the patients.

Author: Three criteria were mentioned in our study for the evaluation of cholecystocholedochal fistula. Among the 21 patients with cholecystocholedochal fistula, four patients fulfilled all three criteria, 11 patients fulfilled two criteria, and five patients fulfilled only one criterion. One patient with cholecystocholedochal fistula did not meet any of the criteria in our study. In previous studies, the diagnosis of cholecystocholedochal fistula was based on X-ray findings of the direct contrast medium filling the fistula to the gall bladder. However, to enhance the cholecystocholedochal fistula, one needs more effort to inject the contrast medium, which is usually avoided by the endoscopist to prevent post-ERCP cholangitis. We think that this could be the reason why the diagnosis rate of cholecystocholedochal fistula was low in previous studies. In our study, we described one additional finding on X-ray (common bile duct (CBD) stricture length > 2 cm for exclusion) and one additional finding on endoscopy view (pus in CBD for inclusion). With this additional information prior to surgery, we think the surgeon could make a more accurate surgical plan.

#2, Related to #1, the authors should show the diagnostic approach of MS patients, including other modalities such as MRCP, CT, etc. Please show the preoperative

[在此鍵入]

detection rate of cholecystocholedochal fistulas by other modalities.

Author: For the pre-operative diagnosis, all patients who underwent ultrasonography initially revealed stones in the gall bladder. Ninety patients further underwent computed tomography (CT) and 85 patients showed a dilated intrahepatic or extrahepatic bile duct before ERCP. Moreover, 24 patients underwent magnetic resonance cholangiopancreatography (MRCP), 20 patients showed an external compression of the hepatic ducts and were suspected to have Mirizzi syndrome (MS). Among the 21 patients with MS with cholecystocholedochal fistula, MRCP was performed in four patients but none of the patients could be diagnosed with a cholecystocholedochal fistula on MRCP.

We have listed the results in the manuscript.

#3. I am interested in how many patients with 3 findings; pus in the common bile duct, gallbladder opacification, and stricture length of CBD less than 2cm had cholecystocholedochal fistulas among patients not to identify fistulas by ERCP alone. The authors should enhance the advantage of those 3 findings.

Author: There was only one patient without any of the criteria mentioned in our study who had a cholecystocholedochal fistula during cholecystectomy. Theoretically, the gall bladder in patients with MS will be enhanced during ERCP if there is a cholecystocholedochal fistula with large amounts of contrast medium. As previously mentioned, the endoscopist usually aims to inject less contrast medium to avoid post-ERCP cholangitis, especially since many of the patients suffered from bile duct infection

[在此鍵入]

before ERCP. Hence, this may be why previous studies were not able to diagnose cholecystocholedochal fistula. In patients with MS, we always focus on the enhancement of the cystic duct, the CBD, and the gall bladder; this was also the original purpose for ERCP in patients with MS. We tend to divide all the factors into two parts, the cystic duct & gall bladder opacification (original purpose) in one part and the other factors in another part (additional finding). We identified four additional findings on endoscopy and cholangiogram that were not previously mention in other studies: pus in the CBD, duodenal ulcer, CBD retrieval, and stricture length of the CBD > 2cm in the logistic regression. There were two factors (pus in the CBD and stricture length of the CBD > 2cm) that were significant. These findings could help surgeons to keep the possibility of cholecystocholedochal fistula before surgical planning. We have adjusted these in the main text and in Table 3.

Table 3. Predictors of cholecystocholedochal fistulas in patients with Mirizzi syndrome

Variate	Univariate OR	p value	95% CI for OR	Multivariate OR	p value	95% CI for OR
Stricture length > 2 cm	0.14	0.01	0.03 - 0.64	0.12	0.008	0.03 - 0.58
CBD stones retrieved	0.25	0.08	0.06 - 1.17			
Pus in the CBD	4.91	0.002	1.77 - 13.59	5.82	0.002	1.93 - 17.58
Duodenal ulcer	1.62	0.38	0.56 - 4.73			

#5. The authors should show complications related to ERCP.

Author: There were three patients who suffered from mild pancreatitis post-ERCP and recovered in one week. We have included this in the manuscript.

[在此鍵入]

Minor:

#1 There are some mistypes, missing an article. In title page and core tip, Mirizzi syndrome In AIMS of the abstract, before cholecystectomy, etc.

Author: We have corrected the mistakes in our manuscript.

Reviewer #2 ID: 03722267

Thank you for your kind recommendations.

Major comments: (1) & (2)

Author: The sample size calculation for logistic regression is based on the work of Peduzzi et al. (1996)^[1] which suggested that a number of events per variable (EPV) greater than ten was stable for prediction. There are three factors in our study and the EPV was seven. However, some studies argued that the “one in ten rule” is too conservative in recent years^[2]. To observe the cystic duct and the gall bladder enhancement was the original purpose of ERCP in patients with MS. We have revised our findings and only put the additional findings into the logistic regression. We used four additional findings never mentioned in other studies as independent factors to aid in the diagnosis of cholecystocholedochal fistula: pus in the CBD , duodenal ulcer, CBD stones retrieval, and stricture length of the CBD > 2cm. We put these four factors into logistic regression and there were two factors (pus in the CBD and stricture length of the

[在此鍵入]

CBD > 2cm) that were significant and also fit the one in ten rule (two factors for 21 events). We have revised Table 3 and have adjusted the manuscript.

#3 How did the author determine the cutoff of the stricture length of CBD >2cm?

Author: We estimated the cutoff for the stricture length of the CBD by the AUROC method and 2 cm showed the best result. Another reason we decided 2 cm as the cut-off level was because we always measure the stricture length by a well-known diameter under X-ray, such as the width of the endoscope or the height of the vertebral body. The mean body height of the individual vertebrae T10-T12 (at the level we often see during a cholangiogram) is about 2-2.2 cm^[3] We can therefore evaluate the length of the stricture quickly by comparing it to the height of the vertebral body.

#4 In the Discussion section, the authors described that after cholecystocholedochal fistula formation, the gallbladder and cystic duct decompress, and the stricture of the CBD may result from the direct compression by the stone, shortening the stricture length (Figure 3). Therefore, the association between stone size and stricture length of CBD may be important in predicting cholecystocholedochal fistulas in patients with MS. The authors should show the association between stone size and stricture length of CBD as a predicting factor.

Author: Due to the retrospective nature of the study, we could not find the actual stone size in our case series. Previous studies in Europe have revealed that the stone size in

[在此鍵入]

patients with MS with a cholecystocholedochal fistula was larger (median 2.25 cm) than in those without a cholecystocholedochal fistula (median 1.5 cm). Due to the differences observed during ERCP in patients in our study, we hypothesized that the stricture caused by Mirizzi syndrome in patients without a cholecystocholedochal fistula may be related to the compression of the gall bladder or the cystic duct, and not due to the stones themselves. The CT image on Figure 3 has also proved our hypothesis.

Minor comments: (1) It is difficult to read the Results section. The author should list the results by headings. (2) Round the numbers to one decimal place (e.g., 6.208 should be revised to 6.2). If the P-value exceeds 0.01, enter no more than two significant digits (e.g., “P = 0.149” should be revised to “P = 0.15”).

Author: We have corrected these mistakes in the results section.

Reviewer 3 ID: 00504581

This is a retrospective and relatively large study of MS patients, diagnosed and treated by ERCP- This interesting paper give us important clues for the diagnosis of severity of MS, because of the presence of a biliary fistula However, there is some missing information that the authors should include in this paper to improve the information Firstly the authors do not speak about the diagnostic tools of MS in their cohort of patients, and specifically about the role of Magnetic resonance cholangiopancreatography (MRCP) as a diagnostic tool before the ERCP. Could you

[在此鍵入]

comment on something about what information did you get with the MRCP before the ERCP procedure? Did MRCP help you in the diagnosis of the presence of a biliary fistula? The second one "... (18 patients received endoscopic nasobiliary drainage and 99 patients received endoscopic retrograde biliary drainage)." Could you give us more information about the types of endoscopic retrograde biliary drainage employed, are you talking about plastic stents (size?) covert metal stent (size?), could you give as more information about the final endoscopic outcome. Did the therapeutic ERCP resolve some MS without biliary fistula? It would be interesting to add some information about the final surgical outcome (when the patients were operated, what type of surgeries were performed and so on) These two paragraphs seem to say the opposite "... a stricture length longer than 2 cm at the CBD is another important endoscopic finding in MS patients without a fistula. Theoretically, the stricture length of the CBD is longer in MS patients with a cholecystocholedochal fistula. " Could you write more clearly please?

Author: Thank you for your kind recommendation. The patients with MS in our study had clinical symptoms, such as jaundice or cholangitis, and therefore most of the patients were referred for an ERCP directly after CT or sonography. Only four patients with MS with cholecystocholedochal fistula underwent MRCP as these patients could not be diagnosed prior to ERCP.

We used endoscopic retrograde biliary drainage (ERBD) (with plastic stents 8.5Fr. or

[在此鍵入]

10Fr. in diameter and 5 cm or 7 cm in length) for the bile duct diversion. All patients in our study underwent cholecystectomy and the fistulas were corrected during the surgery. There were several patients with MS and suspected cholecystocholedochal fistula during ERCP who did not accept surgery post-ERCP as they had no symptoms after ERBD removal during later ERCP examination. All these cases were excluded in our study as we could not confirm the diagnosis of cholecystocholedochal fistula during the surgery.

Due to the retrospective nature of the study, we could not find the actual stone size in our case series. Previous studies in Europe revealed that the stone size in patients with MS with a cholecystocholedochal fistula was larger (median 2.25 cm) than in those without a cholecystocholedochal fistula (median 1.5 cm). Due to the differences in our observation (long CBD stricture often seen without cholecystocholedochal fistula) on cholangiogram, we hypothesized that the stricture in patients with Mirizzi syndrome without a cholecystocholedochal fistula may be related to the compression of the gall bladder or the cystic duct, and not by the stones themselves. The CT image in Figure 3 also proved our hypothesis.

[在此鍵入]

Reviewer 4 ID: 01799105

Thank you for your kind recommendations.

#1 The authors should clarify this sentence: "18 patients received endoscopic nasobiliary drainage and 99 patients received endoscopic retrograde biliary drainage)"

Author: We have added more information about the patients who have received ERBD with plastic stents 8.5Fr. or 10Fr. in diameter and 5 cm or 7 cm in length) for bile duct diversion in our manuscript.

#2 The part related to duodenal ulcers in MS is not-withstanding. It and relevant references should be deleted.

Author: In order to enrich the manuscript, we have decided to keep the mentioned part; however, we have deleted redundant words as per the reviewer's suggestion.

1 Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis.

Journal of clinical epidemiology 1996; **49**(12): 1373-1379

[在此鍵入]

- 2 van Smeden M, de Groot JA, Moons KG, Collins GS, Altman DG, Eijkemans MJ, Reitsma JB. No rationale for 1 variable per 10 events criterion for binary logistic regression analysis. *BMC medical research methodology* 2016; **16**(1): 163
- 3 Chen H, Schlösser TP, Brink RC, Colo D, Van Stralen M, Shi L, Chu WC, Heng P-A, Castelein RM, Cheng JC. The Height-Width-Depth Ratios of the Intervertebral Discs and Vertebral Bodies in Adolescent Idiopathic Scoliosis vs Controls in a Chinese Population. *Scientific reports* 2017; **7**: 46448