

Dear Colleagues,

We appreciate your constructive comments regarding my manuscript. We think that the revisions have been addressed and make this a stronger paper.

Reviewer A:

1 and 2. All patients had suspected choledocholithiasis based on history of gallstones by imaging and labs or imaging consistent with CBDS. Patients that underwent ERCP for indications other than CBDS were not part of this study.

Clarified clinical definition used for suprapapillary stenosis and papillary stenosis. Sphincterotomy was part of all of the procedures at time of CBDS evaluation-ERCP.

3. The time from presentation to procedure varied by several days and that was based on labs. Interestingly, the peak labs for patients were not useful as was pointed out in the GIE reference... As many pediatric patients receive sedation for MRCP, balancing the additional sedation and staff availability was there. Our staffing has changed since these patients were enrolled. This population is a double edged sword and on the great challenges in evaluating these patients. In our experience, 84% of patients had stones at ERCP amongst all patients, ~70% in the GIE 2015 paper. A prospective study evaluating patients evaluated for ERCP for suspected choledocholithiasis and a third arm with those not receiving ERCP based on suspected passed stone would be valuable.

4. Discussion about MRCP and positivity in those patients added.

5. When hemolytics removed, conjugated bilirubin was still significant and differences were still important. The lab trends and imaging of the hemolytics offer us unique information, but agree that removal for certain assessments is appropriate.

6. Brief description about papillary stenosis and suprapapillary stenosis added

7. Figure redone

8. Removed AUS and replaced with US.

9. Removed unnecessary capitalizations

Reviewer B:

1. Additional discussion on Group S, specifically related to challenges of patients without visualized stone on imaging.

2. Modified conclusion

Reviewer C:

1. EUS discussion added

Reviewer D:

1. Discussion about missed stones and risks as well as alternative diagnosis consideration.

Added several references to address reviewer comments

Thank you again for consideration of this manuscript

This retrospective study analyzed 44 pediatric patients (6-18 years) with gallbladder in situ hospitalized for evaluation of common bile duct stones (CBDS). The authors used the modified ASGE criteria (conjugated bilirubin >0.5mg% instead of total bilirubin) to predict the presence of CBDS during ERCP examination. As ERCP is an invasive procedure particularly in children, establishment of a pediatric guideline to avoid unnecessary ERCP is very important. Although the aim of this study is important, there are some questions in the methods which may influence the results to be less convincing. My questions and comments of this study are as the followings: 1.As the statement in the discussion, the case number is small, particularly only 7 patients in group 2, selection bias may exist. 2.This study did not describe the indications of ERCP in the patients enrolled for study. Those patients having suspected pancreatobiliary lesion without symptom, or no definite indication for endoscopic treatment may benefit from the guideline to avoid unnecessary ERCP. (All patients had suspected choledocholithiasis, based on history of gallstones by imaging, and labs or imaging consistent with choledocholithiasis. Patients that underwent ERCP for indications other than choledocholithiasis were not included-data available.

The patients in this study seemed to have strong indications for ERCP due to CBDS, papillary stenosis or suprapapillary stricture; all patients had received sphincterotomy, so the controlled group (Group 2) may be not appropriate.

To clarify, all patients had native papilla and had suspicion for CBD stones. Sphincterotomy was performed as part of duct clearance.

3.The timing between abdominal sonogram and ERCP ranged from one to six days, spontaneous passage of CBDS was possible in those patients without CBDS in ERCP, particularly in the three patients with positive MRCP and the 4 patients with gallstones pancreatitis. The authors should address the time between those examination and ERCP in group 2, and how to exclude the possibility of spontaneous passage of CBDS. 4.Small stones in common bile duct may be masked by the contrast medium during ERCP.

The time from presentation to procedure varied by several days and that was based on labs. Interestingly, the peak labs for patients were not useful as was pointed out in the GIE reference... As many pediatric patients receive sedation for MRCP, balancing the additional sedation This population is a double edged sword and on the great challenges in evaluating these patients. In our experience, 84% of patients had stones at ERCP amongst all patients, ~70% in the GIE 2015 paper. A prospective study evaluating patients evaluated for ERCP for suspected choledocholithiasis and a third arm with those not receiving ERCP based on suspected passed stone would be valuable.

Besides ERCP, EUS and MRCP were also used as the standard methods to confirm the existence of CBDS (Gastrointest Endosc 2015;82:88-93). The authors should discuss about the role of MRCP in the prediction of CBDS and how to avoid unnecessary ERCP in the cases with positive MRCP. (added)5.Usually the conjugated bilirubin elevates parallel with total bilirubin in biliary obstruction except in the patients with hemolytic or severe parenchymal liver disease. Is there any difference in the result if the authors exclude those 8 patients with hemolytic diseases? The preprocedure conjugated bilirubin

was still statistically significant .02 (with hemolytics excluded), vs. .004 (included). Pretotal bili was .104 vs. 0.029. We excluded the hemolytic patients for the purposes of isolating ALT and AST.

6. The authors should address the diagnostic criteria of papillary stenosis and suprapapillary stricture

7. The quality of Figure 1 is poor, it should be deleted or replaced by table. **(Done)**

8. Please give the full name of AUS under the table 1.

**Done**

9. Some words in the text using capital letter (e.g. BOTH, ANY, AND, OR..) are inappropriate, please correct it. **Done**

Dear Editors: Please refer to the following comments on the paper entitled "ERCP for Pediatric Choledocholithiasis: Assessing the Need for Endoscopic Intervention ( Manuscript NO: 23374)", which is submitted as an original article by Fisherman DS, et al. The authors conducted a retrospective analysis in 44 consecutive pediatric patients who underwent ERCP for suspected choledocholithiasis. They applied the current adult guidelines from the American Society of Gastrointestinal Endoscopy (ASGE) in pediatric patients with suspected CBDS to identify factors that may be predictive in the pediatric population. They concluded that using ASGE guidelines in a series of pediatric patients with suspected CBDS, stones were appropriately identified in the majority of cases, while US was poorly predictive of a sensitivity of 42%. Modified criteria using conjugated bilirubin  $\geq 0.5$  mg/dL instead of total bilirubin performed better at identification of CBDS. Future studies are needed to assess pediatric specific criteria in children including both imaging and laboratory data. In the future, pediatric specific guidelines should be developed to optimize ERCP management in children with suspected CBDS. The paper was well constructed, but I would like to recommend its "minor revision" before considering its publication. The followings are the concerns: 1. In daily practice, it is quite important and challenging to predict the necessity of ERCP for patients suspicious of CBD stones, but without obvious CBD stones in

image exam. Therefore, the authors should have discussion on this point (S-criteria). 2. The conclusion should be revised to be more concrete. It seemed the authors tried to emphasize the direct bilirubin level, rather than the total bilirubin level, was more accurate in predicting the presence of CBD stones. Furthermore, the authors might try to compare the accuracy (sensitivity, specificity, PPV, and NPV) of S-PM between ASGE guidelines and the authors' designed criteria in predicting the presence of CBD stones. Many thanks for your kindly invitation to review this paper. Best regards,

However in practice, deciding on ERCP in those without a visualized stone on initial imaging and mild elevations or normal bilirubin is quite challenging. In this setting both the standard and modified pediatric strong criteria are important. In our subset of patients, the S-PM had a higher sensitivity than the standard criteria, and the same specificity. These criteria are dependent on both abnormal bilirubin and ductal dilatation is quite common in stone related disease.

This manuscript applied the current adult guidelines from the ASGE in pediatric patients with suspected CBDS to identify factors that may be predictive in the pediatric population. It is well designed and performed. In general, the results are credible. Endoscopic ultrasound(EUS)is one of the most credible method for diagnosing CBDS in adult. However, the authors failed to mention the role of EUS for pediatric patients in the manuscript. (added). EUS was not available at our institution during study period.

The authors performed a single-center retrospective analysis at a tertiary children's hospital. There were 44 consecutive pediatric patients who underwent ERCP for suspected choledocholithiasis. Patients were stratified into those with CBD stones at ERCP. CBD stones were identified in about 4 out of five cases overall. The Very Strong (VS) and Strong (S) ASGE criteria identified the majority of patients ( $p=.0001$ ). The authors state that current adult guidelines identified the majority of pediatric patients with CBDS, but specific pediatric guidelines may improve detection. The manuscript is well data supported and well written. I would

suggest to add some pathogenesis for missed or chronic CBDS. In fact, this is one of the major factors contributing to cholangiocellular carcinoma in adults.

Due to the relative variability in each of the available tests as well as the reported rates of both missed stones at ERCP and rates of stone passage, clinical experience should complement these tools. Consideration of the inherent risks of the procedure with the risks of a retained stone (eg. pancreatitis) is important as well as the possibility of an alternative diagnosis contributing to intraductal stones such as familial intrahepatic cholestasis or sclerosing cholangitis, both carrying malignancy risks. Intrahepatic stone disease has also been linked to cholangiocarcinoma.