**Author's response to reviews**

**Title:** Endoscopic ultrasound yield in patients with intermediate and high likelihoods of suspected choledocholithiasis: a retrospective study from one university-based endoscopy center

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**Author's response to reviews:** see over
**Point by point revision:**

**Reviewer:** (Rabindra Watson)

**Major Compulsory Revisions:**

1. **Line 137:** this sentence imply that all patients underwent ERCP even if EUS did not detect stones. In this case? If so, this practice should be explain and justified. Did all patients who were high risk for CBD stone undergo ERCP?

   **Answer:** NO, only the patients with CBD stone detected underwent ERCP, only 4 cases with negative EUS study underwent ERCP (BUT that's because of the surgeon requirement before the laparoscopic cholecystectomy). The rest of the patients who did not detect CBD stone on EUS study were followed up for at least 6 months. The patients who had high risk for CBD stone of whom the initial imaging study (US, CT scan or MRCP) showed definitely retained CBD stone would directly go to ERCP and would not be included in this study. *(the answer were inserted in the text body line 113-115 and 142-148).*

2. **Result:** What percentage of patients presented with abnormal liver chemistries (other than bilirubin) The level of elevation should be reported as this has been shown to be sensitive predictors of CBD stones.

   **Answer:** 71.2% of the patients showed abnormal liver enzymes which the mean SGOT was 169.9±206.9 (range 10-936), mean SGPT was 158.3±203.2 (range 7-1376) and mean level of alkaline phosphatase was 174.3±156.4 (range 36-885). *(the answer were inserted in the text body line 177-183).*

3. **Line 159:** why these 4 patients undergo ERCP despite normal EUS?

   **Answer:** There were 4 patients who showed negative EUS studies, but still underwent ERCP for definite diagnosis because the consulting surgeon requirement (before the laparoscopic cholecystectomy). *(the answer were inserted in the text body line 145-148).*

4. **Line 222:** What is the data from this poster? This should be elaborate as this is the basis for the current investigation. Why are these 7 citations at the end of this sentence when only a single publication was discussed.

   **Answer:** The detail of that poster of Ang et al. was added and there was an error of putting the reference which was already corrected already in the text body line 95-98.

5. **Line 224:** discordant with what?

   **Answer:** Therefore, the chance of CBD stone in the patient presented with high clinical likelihood criteria remained discordant compared to the previous reports. However, we re-write the discussion as the revised version. So, this sentence was removed.
6. **Line 229:** Why the investigators ' results different from the current literature? This should be explained or hypothesized offered?

**Answer:** We postulate that the lower of CBD stone detection rate could be related to the chance of spontaneously passed CBD stone which was reported to be about 15-20% in one week(21), regarded of the longer time interval between the index date of onset and the procedure date. *(this was in the text body line 246-250)*

7. **Line 243:** This is not necessary to be true in all part of the world, and therefore the statement should be restricted to the author's own situation.

**Answer:** We agreed, so we correct it to be ' However, performing EUS is not possible in every hospital particularly in many developing countries.' *(this was in the text body line 257-258)*

8. **Line 249:** This sentence and the remainder of the paragraph simply restates the results. This should be remove and the interpretation of this result should be provided.

**Answer:** We agreed, so we remove that sentence and re-write the discussion.

9. **Line 256:** It is established that alkaline phosphatase is synthesized by biliary epithelium in response to obstruction, therefore the phase should be removed from parenthesis.

**Answer:** We agreed, so we did removed it.

10. **Line 232:** This sentence overstate the study's findings. The authors state hypothesize that the low yield of EUS in their study in due to longer time interval between presentation in endoscopy. Therefore it is inappropriate to conclude that ALL high risk patients should undergo EUS prior to ERCP since most patients will be treated within 7 days in many practice setting.

**Answer** We agreed, so we re-write this conclusion as 'This study demonstrated that the use of clinical criteria alone might not provide robust predictions of the presence of CBD stones in all patients, even those with high likelihoods of having CBD stones. EUS evaluation should be considered for these patients, and particularly for those who cannot undergo ERCP within 7 days of their initial clinical presentation and those who are suspected of being at a high risk of ERCP-related complications, to minimize unnecessary ERCP procedures.' *(this was in the text body line 276-281)*

11. A comparison of those patients who were evaluated within 7 day and > 7 days should be provided. If this is not feasible, then the mean time to presentation should be presented for the study's patients as this is critical to the relevance of the proposed data and conclusion.

**Answer:** The mean time for presentation was 37.6±56.6 days(range 1-420days). *added in the text body line 193-194*

12. **The limitations of this study should be presented and discussion.**
Answer: We agreed. So, we added the discussion about the study limitation as the following: This study was limited because it was a retrospective study of a relatively small number of patients; therefore, the interpretations were restricted to particular areas in which the healthcare situations were similar. Importantly, prospective studies should be undertaken to substantiate the current study’s observations. (this was in the text body line 269-272)

**Minor Compulsory Revisions:**

1. The following sentences' grammar from the introduction should be change to the present tense. The incidence of choledocholithiasis in patients who have a gallstone, those who were underwent previous cholecystectomy, and those with acute biliary pancreatitis was 10-20%, 7-14% and 18-33%, respectively.

Answer: We did change it in line 68.

2. Line 94: was lesser would be replaced by 'is less'

Answer: We rewrote the sentence.

3. Line 120: This sentence should be removed and Figure 1 associated with previous sentence.

Answer: We rewrote the sentence.

4. Line 188: Citation of this percentage should be listed. If this data is from the literature, the present tense should be used.

Answer: These numbers were from the present study. (we corrected it in line 183-186)

5. Discussion first paragraph: the present tense should be used when referring to the current medical literature.

Answer: We did correct it in line 219.

6. Line 191: MRPC had less sensitivity compared to what?

Answer: We correct it as in line 218-222.

7. Line 224: The phase " as mentioned above" should be removed.

Answer: We did remove it already.


Answer: We re-wrote it.

**Discretionary Revision:**
1. Line 93: the phase 'a poster presented at DDW' should be omitted and the data simply stated.

Answer: We added the details of this poster as line 95-98

Reviewer (Vani Konda)

Major Compulsory Revisions:

1. Could we get more information on the baseline population. Is the population of patients who underwent EUS generalized to all of the patients presenting with suspicious of choledocholithiasis in their institution? There were 93 patients who underwent EUS and had suspicious of a stone, but does this make up most or a few of all the patients with suspicious for a stone? Do we known if most of the high likelihood patients went straight to ERCP and bypassed the EUS at this institution? Was the ratio of intermediate vs high likelihood similar to those who underwent EUS and those did not.

Answer: In our institute, all the patients who presented with moderate or high likely hood of CBD stone with definite, initial, imaging studies showed CBD stone underwent ERCP. By the way, the patients in this study was the patients who presented with moderate and high likely hood of CBD stone, but the imaging studies were inconclusive. From a total of 914 cases of the patients underwent ERCP with indication of 'CBD stone' during this period (June 2009-Jan 2012), only 93 were enrolled in this study. (This was added in the text body: line 113-115 and 142-148)

2. The study utilized ERCP as the gold standard for the diagnosis of CBD stones. However, not all the patients had the gold standard test. They provided some follow up data but more needs to be in place to have the follow up data be a robust enough reference standard for those patients who had not undergo ERCP. How many patients were followed up or lost? What was the range and median time of follow up. Was there any follow up imaging performed? Were lab values available on all these patients. Are all patients who may subsequently passed a stone but not present to the hospital captured? Since this essence if the reference standard that the authors need to rely on to determine if there is a false negative, more convincing detail needs to be provided.

Answer: Regarded of the retrospective study, there were some limitation of data collection. That practically, we would not bring the patients who showed negative EUS study to undergo ERCP. However, we try to verified the accuracy of the conclusion of negative study by clinical and blood chemistries (with and without imaging studies) followed up. The mean followed up time was 10.2 ±7.9 months (rage from 1-41 months). There were 34 patients(36.6%) who lost to followed up before 6 months But, ALL of them was called to ask and verified the possible
abnormal symptoms which might related with CBD stone. (This was added in the text body: line 187-197)

(By THE WAY, the sensitivity and specificity, PPV, NPV of EUS for diagnosis of CBD stone in this study was calculated from 33 cases of whom underwent ERCP ONLY.)

3. For the sensitivity, specificity, PPV and NPV, could the authors please add the raw numbers of the numerator and denominator in parenthesis? If adequate reference standard is not achieved on those patients who have not undergone ERCP then there should be caution in reporting the diagnostic parameter.

**Answer:** The sensitivity and specificity, PPV, NPV of EUS for diagnosis of CBD stone in this study was calculated from 33 cases of whom underwent ERCP only. (we added as in line 187-197).

4. There is no statistic section.

**Answer:** We agreed, so that we add the statistical section as in line 159-167.

**Minor Essential Revision:**

5. I found the time comparison with the 7 day cut off difficult to follow in the current table. It may deserve its own table with the data more clearly present.

**Answer:** We agreed to change the table 2 and added table 3 as recommended.

6. I found the reference for the poster presented at DDW 2011 difficult to identified. Was this from the author's institution? If so, could more detail be provided.

**Answer:** This poster was not from our institute, anyway, the details regarded this poster were added in the text body line: 95-98

7. Limitations of the retrospective nature of study and lack of gold standard presented on all patients needs to be addressed.

**Answer:** We agreed so, that we added this in the text body as line; 269-272

8. Some of the back ground and discussion are redundant. Could the authors save the comments of other studies for the discussion?

**Answer:** We try to make it not redundant by re-write and re-edit (English editing) already.
We try our best to revised and edited the manuscript regarded all the reviewers' comment. Please find the attached file of revised version (highlight and non-highlight copy).

Best Regards,

Varayu Prachayakul et al.