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*Prospective Study*

**Role of Endoscopic Ultrasound in Evaluation of Patients with Missed Common Bile Duct Stones**

Missed Common Bile Duct Stones by EUS

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## **Abstract**

### **BACKGROUND**

Choledocholithiasis develops in up to 20 % of patients with gall bladder stones. The challenge in diagnosis usually occurs with small stones that may be missed by magnetic resonance cholangiopancreatography (MRCP). Endoscopic ultrasound (EUS) is accurate in detecting CBD stones missed by MRCP, especially the small ones or those impacted at the distal CBD or the papillary region.

### **AIM**

We evaluated the accuracy of EUS in detecting CBD stones missed by MRCP.

### **METHODS**

Patients with an intermediate likelihood of choledocholithiasis according to ESGE guidelines and those with acute pancreatitis of undetermined cause were included. The presence of choledocholithiasis was evaluated by MRCP and EUS, and then results were confirmed by Endoscopic Retrograde Cholangiopancreatography (ERCP). The sensitivity and specificity of EUS and MRCP were compared regarding the presence of stones, the size, and the number of detected stones.

### **RESULTS**

90 out of 100 involved patients had choledocholithiasis, while 10 patients were excluded as they had pancreatic or gall bladder masses during EUS examination. In choledocholithiasis patients, the mean age was  $52.37 \pm 14.64$ , and 52.2% were males. Most patients had biliary obstruction (74.4%), while only 23 (25.6%) patients had unexplained pancreatitis. The overall prevalence of choledocholithiasis was 83.3% in EUS, 41.1% in MRCP, and 74.4% in ERCP. Also, the number and size of CBD stones could be detected accurately in 78.2% and 75.6% by EUS and 41.1% and 70.3% by MRCP, respectively. The sensitivity of EUS was more than MRCP (98.51% *vs* 55.22%),

and their predictive value was statistically significant ( $P < 0.001$ ). Combination of both tools raised the sensitivity to 97.22% and specificity to 100%.

## CONCLUSION

EUS could be a useful tool in assessing patients with suspected choledocholithiasis especially if combined with MRCP. However, its usefulness depends on its availability and the experience of the local centers.

**Key Words:** Keywords: Magnetic resonance cholangiopancreatography; Endoscopic ultrasonography; Choledocholithiasis; Missed CBD stones.

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**Core Tip:** Still, there is a great challenge in diagnosing intermediate probability cases of choledocholithiasis that could be developed in up to 20 % of patients with gall bladder stones. EUS can easily detect small stones that MRCP could miss. EUS still has many diagnostic purposes with high accuracy in detecting CBD stones missed by MRCP, especially the small ones or those impacted at the distal CBD or the papillary region.

## INTRODUCTION

Choledocholithiasis is considered one of the most important causes of abdominal pain in patients with gall bladder stones. It can occur in 3 % - 16 % of patients with gall stones and can reach up to 21 % in patients with gall stone pancreatitis <sup>1,2</sup>. Diagnosis of choledocholithiasis is not always straightforward <sup>3</sup>. Clinical evaluation and biochemical tests are insufficient to establish a firm diagnosis without reliable confirmatory testing, so MRCP is routinely used to clarify the diagnosis after ultrasound results <sup>4</sup>. ERCP is

now considered the gold standard for diagnosis; however, its invasive nature and complications such as pancreatitis defer use in diagnosis as a first option <sup>5</sup>.

Since its recommendation by ASGE and ESGE guidelines for diagnosing the intermediate likelihood of choledocholithiasis with MRCP, EUS is now widely used to assess the presence of choledocholithiasis <sup>6,7</sup>. <sup>5</sup> Despite its overall high accuracy, the role of EUS in the diagnosis of choledocholithiasis has not been firmly established since EUS is relatively invasive compared with MRCP and CT <sup>8</sup>.

The cause of biliary obstruction is not always detected by the available non-invasive imaging modalities like MRCP and may be detected later during biliary drainage as small stones, so in our study, we evaluated the usefulness and accuracy of EUS in detecting missed stones by MRCP as a cause of biliary obstruction.

## **MATERIALS AND METHODS**

Methodology:

Study design and aims:

This observational cohort study aimed primarily to evaluate the usefulness and accuracy of EUS in detecting missed stones by MRCP as a cause of biliary obstruction.

Patients and recruitment:

This prospective study was conducted on 100 patients recruited from National Liver Institute and Internal Medicine department, Kasr Al-Ainy hospital, for 2 years, from 2019 to 2021. We included patients with dilated CBD (diameter ranging from 6 to 10 mm), those with unexplained elevated liver enzymes, and those with unexplained causes of acute pancreatitis. All patients with cholangitis were excluded from the study and referred for urgent ERCP drainage. Also, we excluded patients with malignant masses found in EUS and confirmed by histopathology. All included patients were above 18 years of age.

Assessment of our patients was performed by liver function tests, serum amylase, lipase, abdominal ultrasound, MRCP, and EUS. ERCP was conducted on all patients for

confirmation of the findings in MRCP and EUS. MRCP was done few days before EUS then ERCP was done later on. The EUS operator was blind to MRCP examination. We followed up with the patients for 3 mo after the procedures clinically and biochemically.

Results from MRCP and EUS were compared with those from ERCP to calculate the sensitivity and specificity of EUS and MRCP in detecting choledocholithiasis in our patients. Also, the accuracy of both MRCP and EUS in detecting the size and number of stones in CBD was evaluated.

Our institution's Research Ethical Committee approved the study, and all patients gave their informed written consent before inclusion in the study, according to the ethical guidelines of the 1975 Declaration of Helsinki.

Examination procedure:

All the patients, after thorough full history taking and clinical examination, were subjected to:

- 1) EUS examination using a linear Echoendoscope Pentax EG3870UTK (HOYA Corporation, PENTAX Life Care Division, Showanomori Technology Center, Tokyo, Japan) connected to an ultrasound unit Hitachi AVIUS machine (Hitachi Medical Systems, Tokyo, Japan). All examinations were performed under deep sedation with IV propofol. For EUS-FNA, we used the Cook 19G and 22G needles (Echotip; Wilson-Cook, Winston Salem, NC). Prophylactic ceftriaxone (1g) was administrated before the procedure.
- 2) ERCP examination was performed using a side view scope Pentax ED-3490TK (HOYA Corporation, Tokyo, Japan). All examinations were performed under deep sedation with IV propofol. Prophylactic ceftriaxone (1g) was administrated before the procedure.

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS software version 20.0 (Armonk, NY: IBM Corp). Qualitative data were described using numbers and percentages. Kolmogorov-Smirnov test was used to verify the normality of distribution.

Quantitative data were described using range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). The significance of the obtained results was judged at the 5 % level.

#### 1 - Chi-square test

It was applied for categorical variables to compare different groups.

#### 2 - Fisher's Exact

Correction for chi-square when more than 20 % of the cells have an expected count of less than 5.

## **RESULTS**

### Results:

After excluding the ten patients with malignancy, the total number of male patients was 47 (52 %), and female patients were 43 (48 %) who were included till the end of the study with mean age  $\pm$  SD  $52.37 \pm 14.64$  years (Figure 1). Patients who fulfilled the criteria of the intermediate probability of biliary obstruction were 67 (74.4 %), while those with unexplained acute pancreatitis were 23 (25.6 %), only 7 patients proved to have CBD stones, all were detected by EUS but only 4 patients were detected by MRCP. No other causes of acute pancreatitis as cystic pancreatic lesions, pancreatic divisum or pancreatic duct stones could be detected by MRCP or EUS. Most patients had elevated liver enzymes (60 %) and direct hyperbilirubinemia (81 %), as shown in Table 1. Abdominal ultrasound showed that 72.2 % of patients had gall bladder stones; meanwhile, only 9 had a history of cholecystectomy with a mean CBD diameter of  $9.13 \pm 2.35$  mm.

Choledocholithiasis was detected in 83.3 % of patients by EUS, 74.4 % in ERCP but only 41.1 % by MRCP. EUS detected the number of stones more accurately than MRCP (95 % vs. 41 %, respectively), as shown in Table 2.

Regarding the size of stones, EUS had more accuracy in detecting stones less than 5 mm (25 cases out of 53 negatives for stones by MRCP), as shown in Table 2.

Both EUS and MRCP were statistically significant in detecting stones with P-value < 0.001, but EUS was more accurate than MRCP, especially in stones less than 5 mm (88.8 % vs. 66.6 %, respectively). The sensitivity of EUS was 98.51 %, while in MRCP was only 55.5 %, but specificity was more in MRCP than EUS (100 % vs. 60.87 %, respectively), as shown in Table 3. Combined EUS with MRCP showed sensitivity, specificity, PPV, NPV and overall accuracy of 97.22, 100, 100, 91.67 and 97.87 respectively (Table 4).

Indeed, there are differences in endoscopic skill between endoscopists so we analyzed the data for expert and non-expert endoscopists as in Tables 5.

We found ten cases considered false negative by EUS, where 6 cases had gravels in EUS, 3 cases had small non-floating stones less than 5 mm, and one case had a stone over the old plastic stent. Figures 3, 4 and 5 showed different forms of detected CBD stones from our patients.

The ten cases with the malignant cause of biliary obstruction were detected by EUS as 7 cases with pancreatic head mass, 2 cases with gall bladder carcinoma, and one with CBD mass (further evaluation with spyglass was performed and diagnosed as cholangiocarcinoma).

## **DISCUSSION**

Discussion:

MRCP has been used to detect biliary obstruction in the last decade, but the cause cannot be detected in many patients <sup>5</sup>. The latest ASGE and ESGE guidelines recommend performing MRCP or EUS for evaluating patients with an intermediate probability of choledocholithiasis. However, it did not recommend one modality over the other <sup>6, 7</sup>. Since the wide use of EUS, many studies have evaluated its role in detecting the cause of biliary obstruction <sup>8</sup>. EUS has high diagnostic accuracy in diagnosing pancreatic diseases and sampling tissues, but its role in diagnosing choledocholithiasis has not been confirmed like in pancreatic diseases <sup>9</sup>.



This study evaluated the accuracy of EUS in detecting CBD stones, especially that missed by MRCP in patients with an intermediated probability of CBD stones and recurrent unexplained pancreatitis. Our study included 100 patients, which is considered a large number compared to other studies like *Rana et al*<sup>10</sup> (40 patients) and *Patel et al*<sup>11</sup> (78 patients), but a small number compared to *Wee et al*<sup>12</sup> who included 593 patients but only 35.3 % of those patients had MRCP (All our patients had MRCP).

Similar to the previously mentioned studies<sup>10, 11</sup>, we found no statistically significant variables regarding clinical and laboratory data that could predict the presence of CBD stones in EUS, MRCP, or ERCP.

In the current study, we found that EUS has higher accuracy in detecting choledocholithiasis than MRCP (88.8 % vs. 66.6 %, respectively) with a higher sensitivity (98 % vs. 55 %, respectively) but lower specificity (60.8 % vs. 100 %, respectively). This lower specificity in EUS might be attributed to the time gap between EUS and ERCP (passed stones), missed gravels during balloon sweeping, and false perception of air as stones in some cases. Many other studies that evaluated the diagnosis of choledocholithiasis by EUS showed variable results regarding sensitivities and specificities. For example, *Jagtap N et al*<sup>13</sup> showed that both sensitivities of EUS and MRCP were similarly high (92 % – 98 %). Also, *Patel R et al*<sup>11</sup> showed that EUS sensitivity and specificity were 93 % and 97.3 %, respectively, but most included patients had a high probability of choledocholithiasis. *Wee D et al*<sup>12</sup> reported sensitivities from 85 % to 100 % for EUS and 73 % to 99 % for MRCP. In a meta-analysis of 5 head-to-head studies comparing EUS to MRCP for choledocholithiasis, the pooled sensitivity and specificity of EUS were 97 % and 90 %, respectively, vs 87 % and 92 % for MRCP, respectively<sup>14</sup>.

Also, *De Ledinghen et al*<sup>15</sup> reported good sensitivity (100 %) but low specificity (62 %) for MRCP in diagnosing choledocholithiasis. Meanwhile, *Materne et al*<sup>16</sup> showed 91 % sensitivity and 94 % specificity for MRCP, close to the values for EUS. The study conducted by *Scheiman et al*<sup>17</sup> reported significantly better results with EUS (sensitivity,

95 %; specificity, 80 %) than with MRCP (sensitivity, 40 %; specificity, 96 %) in diagnosing choledocholithiasis.

Another study compared the accuracy of EUS with ERCP in detecting choledocholithiasis and showed that EUS had sensitivity and specificity of 100 % and 94.7 %, respectively.

One of the reasons for missed stones by MRCP that were detected by EUS was non-floating stones at the papillary region or distal CBD, as this is considered one of the pitfalls in MRCP interpretation, as mentioned by *Irie et al*<sup>18</sup>. Another reason was the stones with a diameter less than 5mm (25 cases detected by EUS vs. only 10 cases detected by MRCP), which predicts the accuracy of EUS in detecting small stones<sup>19</sup>. Also, EUS was superior to MRCP in detecting the number of stones inside CBD (70 cases by EUS vs only 26 by MRCP), which is contradictory to the study of *Aubé et al*<sup>20</sup> that found no significant difference between the two modalities (MRCP detected four of six cases while EUS detected five of six cases).

2 Many studies comparing EUS and MRCP in idiopathic acute pancreatitis have shown that EUS has higher diagnostic yields in idiopathic pancreatitis than MRCP<sup>21</sup>. In this context, EUS should be considered the first choice in diagnosing idiopathic acute pancreatitis<sup>22</sup>. 2 Biliary diseases such as cholelithiasis, choledocholithiasis, microlithiasis, and biliary sludge are the leading cause of idiopathic acute pancreatitis<sup>23</sup>.

In our study,<sup>23</sup> cases with unexplained pancreatitis were evaluated by EUS and MRCP, which showed EUS was more sensitive in detecting stones than MRCP (90 % vs. 78 %, respectively), as only 7 patients proved to have CBD stones, all were detected by EUS but only 4 patients were detected by MRCP, meanwhile no other causes of acute pancreatitis as cystic pancreatic lesions, pancreatic divisum or pancreatic duct stones could be detected by MRCP or EUS. And this finding is in agreement with *Akkuzu et al*<sup>24</sup>, who reported sensitivity of EUS and MRCP in evaluating acute pancreatitis of 89.65 % and 72.4 %, respectively.

Combining EUS with MRCP is very valuable in diagnosis of missed CBD stones than each one alone. In our study, the combination of the two tools raised the sensitivity,

specificity, PPV, NPV and overall accuracy into 97.22, 100, 100, 91.67 and 97.87 respectively.

The main limitation in our study was the financial cost of doing EUS, ERCP, and MRCP for all of the included patients. The second limitation is that we considered ERCP the gold standard in detecting CBD stones. Although it is an accurate modality for detecting CBD stones, some false-negative cases may occur. Small stones may be missed if CBD is under or over-filling with contrast. Minute stones or gravels may be missed during balloon sweeping. Also, in some cases, there was a time gap between ERCP and EUS that might give a chance of passage of small stones out of CBD that could give false-positive results in EUS.

## **CONCLUSION**

Conclusion:

Our study showed that EUS and MRCP are not equal tools in diagnosing choledocholithiasis in patients with an intermediate probability of choledocholithiasis. EUS is more accurate than MRCP in detecting non-floating stones in the papillary region and small stones, especially those less than 5 mm, and defining the size and number of stones. Furthermore, combining EUS with MRCP proved to be very valuable in accurate diagnoses of intermediate probability choledocholithiasis patients.

Recommendations:

- EUS could be a good first option for evaluating patients with an intermediate probability of choledocholithiasis when it is available with good experience.
- Combining EUS with MRCP is recommended for accurate evaluation of patients with intermediate probability of choledocholithiasis if both are available.

## **ARTICLE HIGHLIGHTS**

*Research background*

Choledocholithiasis develops in up to 20 % of patients with gall bladder stones. The challenge in diagnosis usually occurs with small stones that may be missed by magnetic resonance cholangiopancreatography (MRCP). Endoscopic ultrasound (EUS) is accurate in detecting CBD stones missed by MRCP, especially the small ones or those impacted at the distal CBD or the papillary region.

### ***Research motivation***

Still, there is a great challenge in diagnosing intermediate probability cases of choledocholithiasis that could be developed in up to 20 % of patients with gall bladder stones. EUS can easily detect small stones that MRCP could miss. EUS still has many diagnostic purposes with high accuracy in detecting CBD stones missed by MRCP, especially the small ones or those impacted at the distal CBD or the papillary region.

### ***Research objectives***

We evaluated the accuracy of EUS in detecting CBD stones missed by MRCP.

### ***Research methods***

Patients with an intermediate likelihood of choledocholithiasis according to ESGE guidelines and those with acute pancreatitis of undetermined cause were included. The presence of choledocholithiasis was evaluated by MRCP and EUS, and then results were confirmed by Endoscopic Retrograde Cholangiopancreatography (ERCP). The sensitivity and specificity of EUS and MRCP were compared regarding the presence of stones, the size, and the number of detected stones.

### ***Research results***

90 out of 100 involved patients had choledocholithiasis, while 10 patients were excluded as they had pancreatic or gall bladder masses during EUS examination. In choledocholithiasis patients, the mean age was  $52.37 \pm 14.64$ , and 52.2% were males. Most patients had biliary obstruction (74.4%), while only 23 (25.6%) patients had

unexplained pancreatitis. The overall prevalence of choledocholithiasis was 83.3% in EUS, 41.1% in MRCP, and 74.4% in ERCP. Also, the number and size of CBD stones could be detected accurately in 78.2% and 75.6% by EUS and 41.1% and 70.3% by MRCP, respectively. The sensitivity of EUS was more than MRCP (98.51% *vs* 55.22%), and their predictive value was statistically significant ( $P < 0.001$ ). Combination of both tools raised the sensitivity to 97.22% and specificity to 100%.

### ***Research conclusions***

EUS could be a useful tool in assessing patients with suspected choledocholithiasis especially if combined with MRCP. However, its usefulness depends on its availability and the experience of the local centers.

### ***Research perspectives***

- EUS could be a good first option for evaluating patients with an intermediate probability of choledocholithiasis when it is available with good experience.
- Combining EUS with MRCP is recommended for accurate evaluation of patients with intermediate probability of choledocholithiasis if both are available.

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