Comparing cost-effectiveness between endoscopic ultrasound and endoscopic retrograde cholangiopancreatography in diagnosis of common bile duct stone in patients with predefined risks: A study from a developing country

Nisa Netinatsunton, Siriboon Attasaranya, Jaksin Sottisuporn, Teepawit Witeerungrot, Theeratus Jongboonyanuparp, Teerha Piratvisuth, Bancha Ovartlarnporn
NKC Institute of Gastroenterology and Hepatology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkla, Division of Gastroenterology, Department of Medicine, International Hospital, Bangmot, Chom Thon, Bangkok, Thailand

ABSTRACT

Background and Objectives: Endoscopic ultrasound (EUS) achieves results comparable to endoscopic retrograde cholangiopancreatography (ERCP) in the diagnosis of common bile duct (CBD) stone, but studies from the western have shown EUS to be less expensive in patients with intermediate risk for CBD stones. The aim of this study was to compare the costs of EUS and ERCP in the diagnosis of CBD stones in a developing country. Materials and Methods: A prospective study was done with 141 patients with suspected CBD stones, categorized as having high or intermediate risk for CBD stone. All underwent EUS, and the high-risk patients had ERCP after the EUS. For intermediate-risk patients, an ERCP was done at the discretion of the attending physician. The CBD stone was confirmed by ERCP in patients who underwent both EUS and ERCP. Patients who received EUS only were followed up every 3 months for 1 year. The false negative rate in patients with EUS and ERCP was estimated in the clinical follow-up. Result: One hundred and forty-one patients (141: 83 females, 58 males) with a mean age ± standard deviation (SD) of 55.71 ± 18.68 years were recruited. Ninety-four (94) patients underwent both EUS and ERCP. ERCP confirmed the diagnosis in 83 of 85 patients (97.6%) with CBD stone detected by EUS. Forty-seven (47) patients with a negative EUS and no ERCP done were symptom-free during the follow-up. The overall sensitivity, specificity, positive predictive value, and negative predictive value of EUS were 97.6%, 80%, 97.6%, and 80% respectively. An EUS-based strategy for high-risk patients was 15% more expensive than an ERCP-based strategy, but the EUS-based strategy reduced the cost to 37.78% less than the ERCP-based strategy in intermediate-risk patients. The EUS-based strategy was cost-saving when the CBD stone prevalence was less than 52.5%. Conclusion: EUS is safer and less costly than ERCP for CBD stone diagnosis in patients with intermediate risk.

Key words: Common bile duct (CBD) stone, cost, effectiveness, endoscopic retrograde cholangiopancreatoscopy (ERCP)-based strategy, endoscopic ultrasound (EUS)-based strategy

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Address for correspondence
Dr. Nisa Netinatsunton, NKC Institute of Gastroenterology and Hepatology, Hat Yai, Songkhla, Thailand. E-mail: nisasan@yahoo.com
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INTRODUCTION

Common bile duct (CBD) stone is a common entity with a prevalence of 10%-15% in patients with symptomatic gallstones undergoing cholecystectomy. Its symptoms include biliary pain, obstructive jaundice, cholangitis, and acute pancreatitis, and these may induce severe complications in some patients.[1] Diagnostic modalities for CBD stone include transabdominal ultrasound (US), computed tomography (CT) of the abdomen, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasound (EUS). CT and MRCP are noninvasive methods for CBD diagnosis but are not sensitive for detecting stones <5 mm.[2,3] ERCP is the “gold standard” diagnostic and therapeutic tool for CBD stone. However, this procedure is associated with potentially serious complications.[4] EUS has been shown to be a sensitive and accurate method for CBD stone diagnosis with comparable efficacy to ERCP.[5-14] Moreover, EUS is associated with a very low procedure-related complication rate.[7] The advantage of EUS as a diagnostic tool in patients with intermediate risk for CBD stone is that it spares patients with negative EUS results for CBD stone from ERCP.[7,10,12,13] The avoidance of unnecessary ERCPs will also decrease the risk of complications related to this procedure, which is higher than that of EUS.[1,7]

Previous studies have found that an EUS strategy was more cost-effective than an ERCP strategy in CBD stone diagnosis in Western populations.[2,3,7] However, one should note that the EUSSs in these studies[2,3,7] were performed by dedicated and expert endoscopists, and their ability to confidently and accurately detect CBD stones may not represent the real working situation in general.

EUS used as the basis of a CBD stone diagnosis strategy is cost-effective when patients with an EUS negative for CBD stone are spared from ERCP in sufficient numbers to counterbalance the cost of the EUS. There are multiple parameters involved in the cost-benefit analysis of an EUS-based strategy versus an ERCP-based strategy, including the cost of ERCP, cost of EUS, prevalence of CBD stones in the population concerned, the sensitivity and specificity of EUS, and the rates of complications related to EUS and ERCP. These parameters may vary from center to center. The cost of medical care, including investigations, in Western countries is different from that in developing (Association of Southeast Asian Nations) ASEAN countries.[15] Therefore, cost-benefit analyses from Western countries may not be applicable to developing countries.

The aim of our study was to assess the cost-effectiveness of an EUS-based strategy versus an ERCP-based strategy in the diagnosis of CBD stone in patients with intermediate risk for CBD stone in a real working situation in a developing country.

MATERIALS AND METHODS

Selection and categorization of patients

All patients with suspected CBD stone from May 2012 to December 2013 attending the NKC Institute (a tertiary center for endoscopy) of the Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand were recruited for the study. The inclusion criteria included a history of biliary pain or recent cholangitis or acute pancreatitis with at least one of the following:

i) Abnormal liver function test (LFT) including elevation of serum bilirubin, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and/or alkaline phosphatase (ALP) more than twice the upper normal limit; and

ii) Dilation of CBD and/or CBD stone detected by US and/or CT.

All the patients had a US or CT done 1-4 weeks before entry. Patients with unstable hemodynamics or severe coagulopathy and those who did not wish to participate were excluded.

The risks for CBD stone were categorized as intermediate risk when a US/CT showed normal bile duct with abnormal LFT or dilated duct with normal LFT, and high risk when a CBD stone was detected by US/CT or dilated duct with abnormal LFT.[6,7]

This study was approved by the hospital Ethics Committee. Informed consent was obtained before a patient was enrolled in the study.

Procedures

All patients with high risk for CBD stone and with intermediate risk and EUS positive for CBD stone underwent ERCP after the EUS. Patients with intermediate risk and EUS negative for CBD stone had an ERCP done at the discretion of the attending physician [Figure 1].
Both EUS and ERCP procedures were performed on an outpatient basis by a junior staff member (NN, JS, TJ, TW) under the supervision of a senior staff member or by a senior staff member (BO, SA) him/herself. In patients with both EUS and ERCP performed, both procedures were done during the same sedation session.

The EUS examinations were performed with an electronic radial EUS scope by Olympus (Model GF UE 160, Olympus Optical Corporation, Tokyo, Japan) or Fujinon (Model EG 530 UR2, Fujinon Corporation, Tokyo, Japan) under conscious sedation with intravenous midazolam, meperidine, and/or propofol according to our protocol.\(^{16}\) The distal bile duct was examined from the inferior part of the pancreatic head and ampulla region. The extrahepatic bile duct including the distal bile duct, subhepatic region of the bile duct, and gallbladder was examined at the duodenal bulb. Diagnosis of CBD stone was made when the EUS showed a hyperechoic structure within the bile duct with or without posterior acoustic shadow that moved on altering the position of the patient. The number and size of the stone(s) were recorded.

ERCP was performed in a standard manner\(^{4}\) using an Olympus duodenoscope (Model TJF-160) by an endoscopist who had not performed the EUS but was not blinded to the results of the EUS.

CBD stone diagnosis was confirmed by stone(s) detected with balloon sweeping during the ERCP in patients who had their ERCP performed after the EUS.

**Follow-up schedule**

All the patients who underwent an ERCP were contacted by phone on days 1, 3, and 30 after the procedure, and attended an outpatient clinic examination at 2 weeks for assessment of symptoms and complications following their ERCP.

Patients with negative EUS without ERCP had 3-monthly follow-up for 12 months to assess symptoms and LFT.

**Complications**

Complications associated with the ERCP procedure were defined according to the criteria of Cotton et al.\(^{17}\)

**Cost analysis**

The costs of making diagnosis of CBD stone, not including subsequent treatment costs, were analyzed. The cost of ERCP for all patients with suspected CBD stones was calculated and compared with the cost of EUS followed by ERCP. The costs included (1) the mean cost of the EUS and ERCP procedures based on the actual cost in our center, which included the cost of medical staff, disposable materials, drugs, equipment amortization, and maintenance, and (2) costs associated with complications resulting from the procedures.

**Cost of procedures**

The cost of one EUS for the purposes of this study was calculated to be 8321 Thai Baht (THB) (USD 253.4) per patient. The cost of an ERCP procedure, excluding the cost of therapeutic intervention, was 28771 THB (USD 887.9) per patient.

**Costs associated with complications**

The cost of ERCP-related complications was estimated from the actual cost of 6 patients with complications in this study (data shown below in the section of complications).

Another cost involved false EUS positives for CBD stone, causing the patient to be sent for an unnecessary ERCP, subjecting the medical system to additional costs and the patient to the risk of ERCP complications.
On the other hand, false EUS negatives for CBD stones create the risk that the patient will later develop symptoms requiring ERCP in the future, with, again, additional expenses and risks. The ERCP complication rate in this study was used to estimate the incidence of ERCP-related complications in patients who had undergone an unnecessary ERCP and in patients with a false EUS negative for CBD stone who might subsequently require an ERCP. For the purposes of the study, it was assumed that a patient with a false EUS negative would later develop symptoms and require an ERCP at some time in the future. Finally, the total calculated cost of an EUS-based strategy included the total cost of EUSs + cost of ERCPs in true EUS positives for CBD stone + cost of estimated complications related to ERCPs in EUS true positives for CBD stone + cost of unnecessary ERCPs + cost of complications related to later ERCPs in false EUS positives + cost of subsequent ERCPs + cost of estimated complications related to ERCPs in patients with false EUS negatives.

The cost-effectiveness of the EUS-based strategy was calculated by the formula below:

\[
\text{Saving cost} = NT \times (\text{Cost of ERCP} + \text{Cost of complications} \times PC) - \left[ NT \times (\text{Cost of EUS} + \{(SN \times PT) + (1-SP) \times (1-P)\} \times (\text{Cost of ERCP} + \text{Cost of complications} \times PC)) + \text{PT} \times (1-SN) \times (\text{Cost of complications} \times PC)\right].
\]

where \(SN\) = Sensitivity of EUS, \(SP\) = Specificity of EUS, \(NT\) = Total number of patients, \(PC\) = Prevalence of complications, \(P\) = Probability of having CBD stone, \(SN \times PT\) = Number with positive EUS, \((1-SP) \times (1-P)\) = False positive probability, \(1-SN\) = False negative probability, and \(PT\) = Prevalence of CBD stones.

The sensitivity and specificity of EUS in this study were analyzed for both high-risk and intermediate-risk patients who had an ERCP done.

**Statistical analysis**

The performance of the EUS in the diagnosis of CBD stone compared with ERCP was analyzed using a two by two table. Student's \(t\)-test was used for the analysis of numeric variables. The sensitivity, specificity, and positive and negative predictive values were calculated.

### RESULTS

The demographic data, clinical presentations, and laboratory data of all patients are presented in Table 1. A total of 141 patients, 83 females and 58 males, were recruited. The mean age ± standard deviation (SD) of the group was 55.71 ± 18.68 years with a range of 18-88 years. Of the patients, 51% had abdominal pain, 23.4% had jaundice, 25.5% had recent cholangitis, and 18.4% had a history of acute pancreatitis. Gallstones were detected in 93 (65.9%) patients by US or CT, and EUS identified gallstones in 6 additional cases. Sixty-four [64 (45.4%)] patients had CBD stones diagnosed by US or CT.

EUS examinations were completed in all 141 patients (100%). ERCPs were successful in all 95 patients who had an ERCP performed at the same time (100%). In these patients who had undergone both tests, the EUS showed CBD stones in 85 patients and the ERCP confirmed CBD stone in 83 patients (97.6%). In
10 patients with a negative EUS for which an ERCP was then done, the ERCP confirmed the negative finding in 8 patients. Among all patients with both EUS and ERCP, there were two false positive and two false negative diagnoses of CBD stone. Overall, the study sensitivity, specificity, positive predictive value and negative predictive value of EUS were 97.64%, 80%, 97.64%, and 80%, respectively.

The EUS diagnosed CBD stone in 59 of 68 patients with high risk for CBD stone and all were confirmed by ERCP. EUS was negative in 9 patients with 7 cases confirmed by ERCP, so the EUS yielded false negative results in 2 patients [Table 3]. The sensitivity, specificity, positive predictive value, and negative predictive value of EUS for CBD stone diagnosis in the high-risk group were 96%, 100%, 100%, and 77%, respectively [Table 4].

The EUS detected CBD stones in 26 of 73 patients with intermediate risk and the ERCP confirmed these diagnoses in 24 of the 26 patients, leaving two EUS false positive results in this group [Table 3]. The 47 intermediate-risk patients diagnosed as having no CBD stone by EUS were followed up. All these patients had no symptoms and normal LFT every 3 months of follow-up, and all were symptom-free at 12 months. The false negative rate in 95 patients with both EUS and ERCP in our study was 2.1%, so the estimated false negative rate in patients with follow-up was 0.99%, indicating roughly one case with false negative EUS. Based on this assumption, EUS diagnoses for CBD stone were 24 true positive, 46 true negative, 2 false positive, and 1 false negative [Table 3]. Thus the overall sensitivity, specificity, positive predictive value, and negative predictive value of EUS in CBD stone diagnosis in the intermediate-risk group were 96%, 95.80%, 92.30%, and 97.90%, respectively [Table 4].

There were two EUS false negatives for CBD stone: One was due to a stone at the common hepatic duct confluence and the other involved a stone detected by EUS but misinterpreted as negative. Of the two EUS false positives, one was due to a thrombus in the portal vein detected by CT but misinterpreted as a stone, and the other was a hyperechoic lesion in CBD without acoustic shadow but negative ERCP.

The EUS identified an additional diagnosis in 2 patients, 1 with side branch and 1 with main duct pancreatic intraductal papillary mucinous neoplasm (IPMN).

The CBD stones were successfully removed at the first ERCP in 82 (96.4%) of 85 patients. One required one additional ERCP, 1 required laser lithotripsy to remove the stone, and 1 was referred for surgical removal of gallstone and CBD stones.

Complications

There were no EUS-related complications in the 141 cases. Post-ERCP complications occurred in 6 (6.3%) of the 95 patients who underwent ERCP. One patient developed mild pancreatitis with hospitalization for 3 days; two patients developed bleeding from a sphincterotomy, one of whom needed...

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**Table 2. Characterization of study patients by risk group**

| Patients' characteristics | High risk | Intermediate risk | P value |
|---------------------------|-----------|------------------|---------|
| Number (%)                | 68 (48.2%)| 73 (51.8%)       |         |
| Mean age±SD (range) (years) | 59.31±18.94 | 53.14±17.7 | 0.091 |
| Mean total bilirubin±SD (range) (mg%) | 2.13±3.66 | 2.14±3.85 | 0.992 |
| Mean AST (range) | 57.41±57.32 | 62.5±87.6 | 0.679 |
| Mean ALT | 72.35±80.02 | 71.4±83.3 | 0.919 |
| Mean ALP | 211.3±175.9 | 153±120 | 0.022 |
| Number of patients with stones (%) | 59 (86.7%) | 26 (35.6%) | 0.000 |
| Mean stone size (range) (mm) | 11.69±5.11 | 9.03±4.50 | 0.030 |
| Mean CBD size by USG or CT (range) (mm) | 11.39±4.55 | 9.07±3.49 | 0.006 |
| Mean CBD by EUS (range) (mm) | 10.96±3.5 | 7.69±3.11 | 0.000 |

**Table 3. EUS versus ERCP findings**

| EUS | ERCP | Total |
|-----|------|-------|
|     | Positive | Negative |     |
| EUS in high risk | 59 | 0 | 59 |
|   | 2 | 7 | 9 |
| EUS in intermediate risk | 24 | 2 | 26 |
|   | 1 | 46 | 47 |

**Table 4. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of EUS for CBD stones by risk group**

| Patients' characteristics | In 95 with EUS + ERCP (%) | High (%) | Intermediate (%) |
|---------------------------|---------------------------|----------|------------------|
| Sensitivity | 97.64 | 96 | 96.00 |
| Specificity | 80.00 | 100 | 95.80 |
| PPV | 97.64 | 100 | 92.30 |
| NPV | 80.00 | 77 | 97.90 |

PPV: Positive predictive value, NPV: Negative predictive value.
hospitalization for 2 days; two patients with a suspected sphincterotomy-related perforation were admitted but subsequently discharged 3 days later; and one patient developed acute cholangitis due to retained CBD stones, requiring a second ERCP to remove them, with hospitalization for 4 days. The median hospital stay due to ERCP-related complications was 3 days and the mean cost of treatment for complications was 17242 THB (USD 532.2).

**Cost**
The proportion of patients with CBD stone was 89.7% in high-risk patients, and all of these patients required ERCP for stone removal. The EUS-based strategy for the diagnosis of CBD stones in the high-risk group increased the cost substantially compared with the ERCP-based strategy, as calculated by the formula described below:

The saving cost = 68(28771 + 17242 × 0.06) – [68(8321) + {(0.96 × 62) + (1-1)(1-0.89)}(28771 + 17242 × 0.06) + 62 × (1-0.96)(28771 + 17242 × 0.06) + 17242 × (1-1)(1-0.89) × 0.06].

The saving cost = (2026775.36) − [565828 + 1774024.70 + 73917.69] = -386994.88 THB (11944.3 USD).

The EUS-based strategy in the diagnosis of CBD stone in the high risk group increased the cost by 5691.10 THB (175.7 USD) per patient compared to ERCP. The total cost per patient in the EUS strategy was 34462.10 THB (1063.6 USD) compared with 29805.52 THB (919.9 USD) in the ERCP strategy [Table 5].

In intermediate risk patients, the cost effectiveness of the EUS-based strategy was calculated by the same formula. The cost savings per patient of the EUS-based strategy was obtained by substituting the value of each parameter by the value derived in the intermediate risk group.

The saving cost = 73(28771 + 17242 × 0.06) – [8321 × 73 + {(0.96 × P × 100) + (1-0.95) (1-P)} (28771 + 17242 × 0.06) + P × 100 × (1-0.96) (28771 + 17242 × 0.06) + 17242 × (1-0.95) (1-P) × 0.06].

Therefore, zero cost saving = 73 × 29805.52 − [607433 + (96P + 0.05-0.05P)29805.52 + 29805.52 × 4P + (0.05-0.05P) × 17242 × 0.06].

The value of P was 0.525 and the maximum prevalence of stones was 52.5% when the EUS cost saving was nullified.

**DISCUSSION**
The overall sensitivity of 97.6% of EUS for CBD stone diagnosis in the present study was in the range reported by other studies with the pooled sensitivity of 80%-98%.\[1,2,5-7,14\] The overall specificity of 80% of EUS in this study was below the reported pooled specificity of 95%-99% in the literature.\[1,2,5-7,14\] The effect of operator dependency in EUS may account for some of this variance, as the EUSs in our study were performed by different endoscopists, while in many other studies the EUSs were reportedly done by dedicated expert endoscopists.\[1,2,5-7\] There were no EUS-related complications in our study, which conformed with the results of very low EUS-related complication rates in other studies.\[1,7\] The complication

| CBD stone risk       | ERCP cost per patient THB (USD) | EUS cost per patient THB (USD) | Cost saving THB (USD) | Percentage of cost saving (%) |
|----------------------|---------------------------------|-------------------------------|-----------------------|------------------------------|
| High-risk group      | 29805.52 (907.60)               | 34462.10 (1049.40)            | -4656.58 (-141.80)    | -15.62                       |
| Intermediate-risk group | 29805.52 (907.60)             | 18545.23 (564.71)             | 11260.29 (342.89)     | 37.78                        |
The majority of patients in the high-risk group had CBD stones detected by US or CT, and the 89.7% prevalence of stone was approximately three times higher than in the intermediate-risk group in the present study. The EUS-based strategy in this group increased the cost by 15% more per patient compared with ERCP, so the ERCP-first approach seemed to be more cost-effective. However, an earlier study has reported spontaneous migration of stones in about 21% of patients within 1 month without causing symptoms in the majority of cases,[19] and another study found that when the cholangiogram was delayed for more than 1 week, 80% had already passed the stone at the time of the scheduled cholangiogram.[20] Therefore, an ERCP-first approach may be performed in patients at high risk for CBD stone provided that there is only a short time interval of not more than 1 week between the onset of symptoms and the time of the ERCP.[17,19,20] However, further studies are needed to define the optimal interval for the selection of an ERCP- or EUS-based strategy in high-risk patients.

The EUS-based strategy was less expensive than the ERCP-based strategy in the diagnosis of CBD stone in patients with intermediate risk of having CBD stones in this study. Our results confirmed the cost-effectiveness of the EUS strategy in the diagnosis of CBD stones[3] even in the setting of a developing country. The major determinants for the cost-effectiveness of EUS, in addition to the efficacy of EUS in detecting CBD stones, were the cost of EUS compared with ERCP and the prevalence of stones in the population concerned. The higher the cost of ERCP compared with EUS, the greater the cost reduction that will be observed for the EUS-based strategy. The cost-effectiveness of the EUS-based strategy was inversely related to the prevalence of stones. In one study of decision model analysis, it was found that EUS was cost-effective when the accuracy was greater than 90% and the EUS cost was less than 60%-70% of the ERCP cost in intermediate-risk patients.[8] Our study found that the EUS-based strategy was less expensive if the risk of stone was not more than 52%. Our findings were similar to the study of Buscarini et al., which showed that an EUS-based strategy was less costly than an ERC-based strategy in the diagnosis of CBD stone when the risk of CBD stone was not more than 60%.[7] EUS was shown to be a cost-saving strategy based on the cost of CBD stone management in a study with 5 patients, and in another study in patients with low to moderate risk for CBD stone.[24] However, an EUS-based strategy was found to have incurred more expense than ERCP in the management of CBD stone in the study of Prat et al.[9] Unfortunately, the risk stratification criteria in many studies including our study have not been uniform.[5-7] Despite this limitation, an EUS-based strategy for CBD stones seems to be the best cost-saving option in most studies in patients with intermediate risk, and this approach may be justified in centers with an EUS service available.

In addition to the cost savings of an EUS-based strategy, this approach has also been found to prevent the occurrence of ERCP-related complications.[1,6,7,21] The impact of complications due to ERCP on patient productivity, and the physical and psychological burdens to both the patient and the family members are difficult to estimate. One common complication of ERCP is post-ERCP acute pancreatitis, which impairs the quality of life in the general health domain and the vitality domain according to one systematic review.[22] Moreover, EUS provided additional diagnoses not detected by prior imaging. Gallstones were identified in 6 additional cases missed by US and/or CT. The superiority of EUS in detecting gallstones has been reported in the literature.[23] The diagnosis of IPMN in some patients will actually alter the management of the patients. All these advantages of an EUS-based strategy are crucial for the management of patients with intermediate risk for CBD stone. There were some limitations to the study, notably 1) it was a single-center study and thus may not represent other centers in a developing country; 2) there was no blinding of the EUS results to the endoscopist performing the ERCP; and 3) the ERCP was used as the “gold standard,” although at least one study has reported a false negative by ERCP,[24] which could lead to underestimation of EUS accuracy.

CONCLUSION

An EUS-based strategy is comparably reliable, safer, and less costly than an ERCP-based strategy in the diagnosis of CBD stone in patients with intermediate risk.

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There are no conflicts of interest.

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