ACCURACY OF ENDOSCOPIC ULTRASOUND WITH TRANSABDOMINAL ULTRASOUND IN THE DIAGNOSIS OF COMMON BILE DUCT STONE IN UNIVERSITY OF MALAYA MEDICAL CENTRE

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ABSTRACT

Introduction

Choledocholithiasis is a very common condition worldwide and is associated with significant morbidity and mortality. Previously, the diagnosis of choledocholithiasis was made by transabdominal ultrasonography(TAS) followed by endoscopic retrograde cholangiopancreatography (ERCP) if suspicious of choledocholithiasis. Unfortunately, the sensitivity of TAS is low. On the other hand, ERCP carries a high risk of complications and should strictly be reserved only for therapeutic purposes. In the last two decades, endoscopic ultrasound (EUS) has been increasingly used in the diagnosis of suspected choledocholithiasis. Previous studies have shown EUS to be highly accurate compared to transabdominal ultrasound, but at the same time has a much lower complication rate than ERCP.

Objective

Primary Objectives:

- To determine the sensitivity, specificity, positive predictive value, and negative predictive value of EUS in the diagnosis of CBD stones in University Malaya Medical Centre
- To compare the accuracy of EUS vs TAS in patients (who have undergone both procedures) in the diagnosis of CBD stones.

Secondary Objective:

- To assess the positive and negative predictive values of EUS depending on the individual's probability for choledocholithiasis.
- To identify the baseline demography of the patients with confirmed choledocholithiasis and predictive factors for the diagnosis of choledocholithiasis.

Methods

This is a retrospective study where all patients with suspected choledocholithiasis who underwent both EUS and TAS from 2011 to 2016 were recruited. The baseline demography, symptoms, biochemistry, TAS finding and EUS findings were recorded. The final diagnosis of choledocholithiasis was made based on ERCP finding and clinical outcome following a minimum six-month follow up and subsequently the sensitivity, specificity, positive predictive value and negative predictive value for EUS and TAS were calculated.

Results

192 patients were recruited. 93(48.4%) had choledocholithiasis. EUS has the sensitivity of 95.7% and 84.8% specificity; TAS has 41.9% sensitivity and 88.9% specificity.

Conclusions

Endoscopic ultrasonography (EUS) remains high accuracy for detecting choledocholithiasis compared to transabdominal ultrasonography(TAS). In our study, none of the predictors (Age, Ethnicity, Gender, Abdominal pain, Elevated GGT, ALP, AST, ALT, WBC and Amylase) were found to be associated with choledocholithiasis.

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LIST OF ABBREVIATIONS

TAS	Transabdominal Ultrasonography
EUS	Endoscopic Ultrasonography
ERCP	Endoscopic Retrograde Cholangiopancreatography
CBD	Common Bile Duct
CT	Computerized Tomography
MRCP	magnetic retrograde cholangiopancreatography
ALP	Alkaline Phosphatase
ALT	Serum Alanine Aminotransferase
AST	Aspartate Aminotransferase
GGT	G-Glutamyl Transferase
WBC	White blood cell
ASGE	American Society of Gastrointestinal Endoscopy
PPV	Positive Predictive Value
NPV	Negative Predictive Value

CHAPTER 1: INTRODUCTION

Gall stone disease (includes choledocholithiasis or common bile duct stones) is common worldwide. Although most cases are asymptomatic, significant complications include cholecystitis, gallbladder empyema, obstructive jaundice, ascending cholangitis, acute pancreatitis and gallbladder carcinoma can occur. Many of these complications are due to choledocholithiasis or stone(s) in the common bile duct (CBD), which remains a significant health problem and it is associated with high morbidity and some cases of mortality. Previously, the main methods for diagnosing choledocholithiasis was by transabdominal ultrasonography(TAS) and diagnostic endoscopic retrograde cholangiopancreatography (ERCP). The main advantage of TAS is that it is cheap, easy to perform and noninvasive. However, it is operator dependent and CBD is often obscured by bowel gas and fat. Therefore, the diagnosis of probable choledocholithiasis is often made only if the proximal common bile duct and intra hepatic duct are dilated in someone with a typical clinical history (Sakijan and Atan 1987). Diagnostic endoscopic retrograde cholangiopancreatography (ERCP) has the advantage of permitting intervention in the same setting if a CBD stone is present. However, it is invasive and has a high risk of complications such as pancreatitis, perforation, infections and bleeding (Freeman 2012).

Therefore, many noninvasive and more accurate methods of diagnosing choledocholithiasis have replaced diagnostic ERCP include magnetic retrograde cholangiopancreatography (MRCP), endoscopic ultrasonography (EUS) and computerized tomography scan (CT). MRCP is noninvasive and has a higher accuracy than CT and TAS. However, it has slightly lower accuracy than EUS (Yaghoobi, Meeralam, and Al-Shammari 2017; Sugiyama and Atomi 1997) and in our setting the waiting list is long, very expensive and has a variable image quality. Although CT scan

is noninvasive but has a radiation risk and is less accurate than MRCP and EUS (Sugiyama and Atomi 1997). Whereas, EUS is highly accurate in diagnosing CBD stones, especially those <5mm but is also operator dependent and more invasive than MRCP and CT. It may miss stones which are near the porta hepatis. **Table 1.1** summarizes the advantages and limitations of all the investigations.

Table 1.1: Advantages and Disadvantages of TAS, EUS, ERCP, CT, MRCP

	ADVANTAGE	DISADVANTAGE
TRANSABDOMINAL ULTRASOUND	Cheap Non-invasive	Operator dependent Unable to visualize distal common bile duct.
ENDOSCOPIC ULTRASONOGRAPHY	Less invasive than ERCP Excellent on imaging Extrahepatic stones	Limited detection of stones in portal hepatis
ERCP	Can be diagnostic or therapeutic	Unable to proceed if failed cannulation of common bile duct Contrast Complications Higher risk of complications and invasive
CT	Non-invasive	Contrast complications Radiation risk Poor in detecting small stones
MRCP	Non-invasive	Contrast complications Poor in detecting small stones Expensive

EUS was first discovered and initially used in dogs and eventually used in human around 1980s (DiMagno et al. 1980; Dimagno et al. 1982). There are two types of echo endoscopes, radial and linear. Radial echo endoscopes scan 360 degrees and provide images similar to CT scans whereas the linear scope scans in parallel with the scope. The radial scope has the advantage of allowing complete visualization of certain structures such as the CBD without extensive interrogation but the linear scope is essential for interventional procedures such as fine needle aspiration.

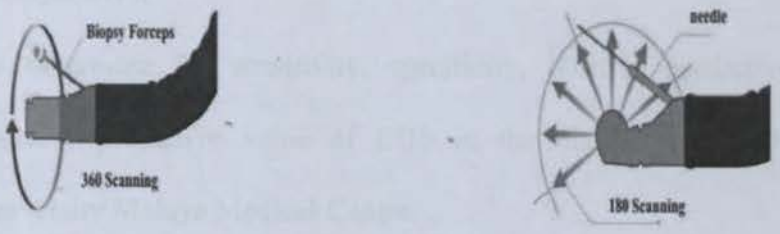

Figure 1.1: Picture from Olympus Europa showing radial and linear EUS

Among one of the most important indications for EUS is that it is good for diagnosing choledocholithiasis. Many studies have shown the sensitivity and specificity of EUS for detecting choledocholithiasis is high (Tse et al. 2008) and is particularly useful in detecting small stones in the CBD as the views are not obscured by bowel gas. Nevertheless, EUS has limitations when it comes to detecting stones in the porta hepatis (Sugiyama and Atomi 1997). In addition, EUS is minimally invasive with low morbidity. Recognized complications include perforations, aspiration, infections, tumor metastasis although the risks are very low (Jenssen et al. 2012)

In Malaysia, EUS was introduced in 2001. ((MGIR) 2009). However, to date, there are only about six centres in Malaysia which perform large volume of EUS. In our centre, EUS has been the standard diagnostic modality for suspected choledocholithiasis for the past 11 years. Generally, all cases of suspected CBD stones will initially undergo a TAS. Most cases will then undergo EUS for confirmation of findings. However, a small number of patients with a high clinical suspicion of choledocholithiasis and a positive TAS will proceed directly to ERCP without undergoing an EUS.

1.1 Aims

Primary Objectives:

- To determine the sensitivity, specificity, positive predictive value and negative predictive value of EUS in the diagnosis of CBD stones in University Malaya Medical Centre.
- To compare the accuracy of EUS vs TAS in patients (who have undergone both procedures) in the diagnosis of CBD stones.

Secondary Objective:

- To assess the positive and negative predictive values of EUS depending on the individual's probability for choledocholithiasis.
- To identify the baseline demography of the patients with confirmed choledocholithiasis and predictive factors for the diagnosis of choledocholithiasis.

1.2 Hypotheses

- EUS is highly accurate in the diagnosis of CBD stones.
- EUS is far superior to transabdominal ultrasonography in diagnosing CBD stones.
- The introduction of EUS precludes the need for diagnostic ERCP, thereby reducing the ERCP associated complications.
- The positive and negative predictive value of EUS depends on the risks of the individual developing choledocholithiasis.

CHAPTER 2: METHODS

This study was approved by the University of Malaya Medical Centre ethics committee and carried out in accordance with the Declaration of Helsinki.

All patients who underwent EUS for suspected choledocholithiasis in University Malaya Medical Centre in the past five years were retrospectively recruited. Baseline demography, symptoms and biochemistry of the patients were recorded, as well as the TAS and EUS findings. The diagnosis of choledocholithiasis is based on the following;

ERCP finding of choledocholithiasis and/or

Clinical course on follow up a minimum of 6 months after EUS (i.e. whether or not patient was subsequently found to have choledocholithiasis). This involves outpatient follow up either in the gastroenterology or hepatobiliary surgical clinic where the patient was assessed clinically for abdominal pain, jaundice as well as liver function tests plus or minus repeat imaging (CT, EUS) if indicated.

2.1 Exclusion criteria:

Patients who did not have complete data (for example both TAS and EUS findings and did not have complete notes for up to six months following the index EUS) were excluded.

Cases where the final diagnosis was stone or stones in the biliary system but out of the CBD (for example stones in the intrahepatic ducts or in the cystic duct causing compression of the CBD (Mirrizi's syndrome) were excluded.

2.2 Definitions:

TAS was considered positive when either there is dilated CBD (>0.6mm) or stone(s) in the CBD documented.

EUS was considered positive when at least one stone was seen in the CBD.

ERCP was considered positive where the cholangiogram showed stones in the CBD or documented stones were extracted.

Charcot's Triad was defined as presence of fever, jaundice and abdominal pain.

Table 2.1: ASGE predictors of Choledocholithiasis (Committee et al. 2010)

Very Strong	
CBD stone on transabdominal ultrasonography	
Clinical ascending cholangitis	
Bilirubin more than 4mg/dL (30.78umol/dL)	
Strong	
Dilated CBD on transabdominal ultrasonography	
Bilirubin 1.8-4mg/dL (30.78-68.4umol/dL)	
Moderate	
Abnormal liver biochemical test other than bilirubin	
Age older than 55 years	
Clinical gall stone pancreatitis	
Likelihood of choledocholithiasis based on	
Presence of any very strong predictor	High
Presence of both strong predictors	High
No predictor	Low
All other patients	Intermediate

2.3 Biochemistry

The normal ranges for the relevant laboratory tests in our hospital were defined as follows: Total Serum Bilirubin, 3-17umol/L; Conjugated Bilirubin, 0-3umol/L; Serum Alkaline Phosphatase (ALP), 50-136U/L; Serum Alanine Aminotransferase (ALT),12-78U/L; Aspartate Aminotransferase (AST), 15-37U/L; Serum G-Glutamyl Transferase (GGT), 15-85U/L; Serum Amylase, 25-115U/L; White Blood Cell (WBC), 4-10.0 10^9. Any values above the normal values were considered abnormal.

2.4 Statistical analysis:

Data were analyzed using SPSS version 23. Standard parameters of descriptive statistics used for baseline characteristics of variables. Univariate analysis to identify the factors of association of choledocholithiasis, and if the p-value of less than 0.1, then a multivariate analysis, logistic regression by backward elimination were used to determine the adjusted odds ratios for the Predictive factors. P-value of less than 0.05 in multivariate were considered significant.

2.5 EUS procedure

Informed consent was obtained from all patients. EUS was performed either by a trained endosonographer or by a trainee under the supervision of a consultant with the patient in left lateral decubitus position. The patient is under conscious sedation (2.5-5mg of midazolam and 500-1000mcg of fentanyl). In almost all cases, the radial EUS is used. In the absence of duodenal stenosis, the echo endoscope is passed into the lower part of the second segment of duodenum. As the ultrasound probe is only 1-2 cm far from the bile duct, very detailed images were usually possible to be obtained.

Figure 2.1: Picture of dilated CBD duct with a stone in a radial EUS. (Gastroenterology unit, PPUM)

Figure 2.2: Picture of a non-dilated CBD duct with a stone in a radial EUS

(Gastroenterology unit, PPUM)

CHAPTER 3: RESULTS

There were 329 patients who underwent EUS for suspected CBD stones between 2011-2016 but 137 were excluded from analysis due to incomplete data, therefore analysis was carried out on 192 number of patients.

The baseline demography was as follows; 93(48%) were male, 99(51%) were female. Mean age was 56.14±16.25. Breakdown according to ethnicity was as follows; Malay 84 (43.8%), Chinese 69 (35.9%) and Indian 32 (16.7%). For the presenting symptoms, 158 (82%) had abdominal pain, 90 (46.9%) had jaundice, 64 (33.3%) had fever, 63 (32.8%) had vomiting. Biochemically, 160 (83%) had a raised total bilirubin. When the bilirubin levels were categorized based on ASGE guidelines, 68(35%) patients had total bilirubin less than 1.8mg/dl or 30.78umol/dL; 63 (32.8%) had total bilirubin between 1.8-4mg/dL or 30.78-68.4umol/dL and 61 (31.8%) had more than 4mg/dL or 68.4umol/dL. 159 (82.8%) had raised alkaline phosphatase (ALP), 158 (82.3%), 168 (87.5%) and 188 (97.9%) had raised ALT, AST and GGT respectively. 97 (50.5%) had high amylase and 121 (63%) had high WBC. Thirty-eight (19.8%) had Charcot's Triad positive. 114 (59.4%) patients had high risk, 72 (37.5%) had intermittent risk and 6 (3.1%) had low risk.

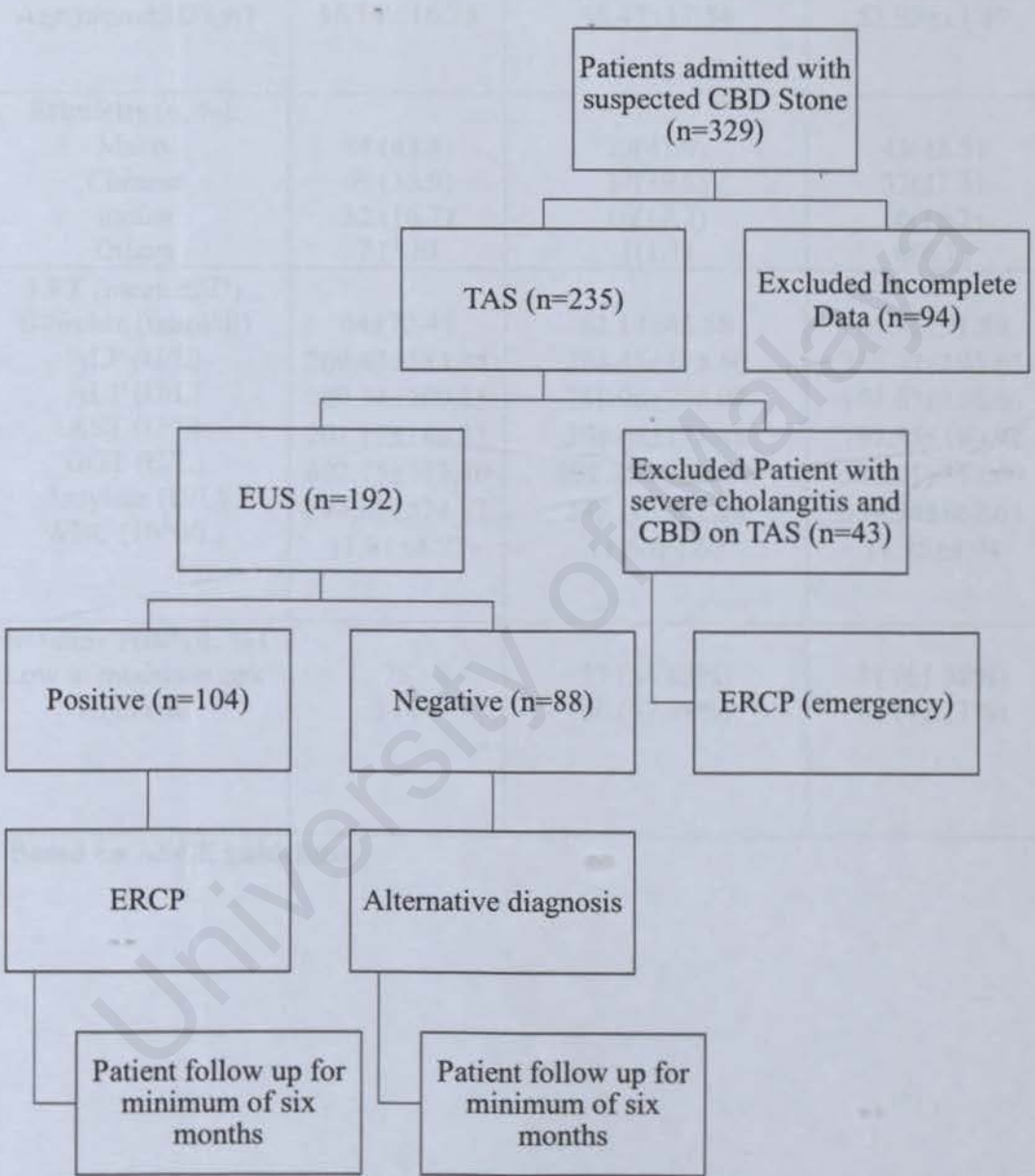

Figure 3.1: Patient Flow Chart

Table 3.1: Baseline Demography

Patient characteristics	Total patients	Choledocholithiasis	No Choledocholithiasis
Sex: Male (n, %) Female (n, %)	93 (48) 99 (51)	48(51.6) 45(48.4)	45(45.5) 54(54.5)
Age(mean±SD)(yr)	56.14 ±16.25	58.47±17.54	53.95±14.69
Ethnicity (n, %): Malay Chinese Indian Others	 84 (43.8) 69 (35.9) 32 (16.7) 7 (3.6)	 39(41.9) 37(39.8) 16(17.2) 1(1.1)	 45(45.5) 32(32.3) 16(16.2) 6(6.1)
LFT (mean ±SD) Bilirubin (umol/dl) ALP (U/L) ALT (U/L) AST (U/L) GGT (U/L) Amylase (U/L) WBC (10^9/L)	 64±72.44 269.43±184.25 240.34±209.25 201.15±186.23 697.75±773.40 294.03±574.87 11.81±4.77	 62.14±43.58 284.45±173.50 288.96±238.07 204.66±171.48 891.22±1015.56 245.16±462.28 11.66±4.60	 65.75±91.86 255.32±193.63 194.67±166.66 197.85±199.92 516.01±358.69 339.94±662.63 11.95±4.94
Baseline risk*(n, %) Low to moderate risk High risk	 78 114	 27 (34.62%) 66 (57.89%)	 51 (65.38%) 48 (42.11%)

***Based on ASGE guidelines**

3.1 Accuracy of EUS and TAS for choledocholithiasis

EUS detected CBD stones in 104 (54.2%) and TAS in 50 (26.0%). 93 were eventually found to have CBD stones on ERCP or clinical follow up. The sensitivity, specificity, positive predictive value and negative predictive value in the diagnosis of CBD stones by Transabdominal ultrasonography (TAS) were 41.9%, 88.9%, 78% and 62.0% for TAS. The sensitivity, specificity, positive predictive value and negative predictive value of EUS in the diagnosis of CBD stones were 95.7%, 84.8%, 85.6% and 95.4% for EUS.

3.2 Baseline demography of patients with CBD stones and predictive factors for choledocholithiasis

Looking specifically at patients with confirmed choledocholithiasis, 48 (45.5%) were males, 45 (48.4%) were females. In terms of ethnicity, 39 (41.9%) were Malays. 37 (39.8%) were Chinese and 16 (17.2%) were Indians. Mean age was 58.47±17.54.

For the presenting symptoms, 81(87.1%) had abdominal pain, 52 (55.9%) had jaundice, 30 (32.3%) had fever, 33 (35.5%) had vomiting. Biochemically, Total of 85 (91.4%) had raised Total Bilirubin by our biochemical normal range. However, if according to ASGE guideline, 25(26.9%) patients had total bilirubin less than 1.8mg/dl or 30.78umol/dL; 38 (40.9%) had total bilirubin between 1.8-4mg/dL or 30.78-68.4umol/dL and 30 (32.3%) had more than 4mg/dL or 68.4umol/dL. 83 (89.2%) had raised Alkaline phosphatase (ALP), 82 (88.2%), 85 (91.4%) and 92 (98.9%) had raised ALT, AST and GGT respectively. 42 (45.2%) had high amylase and 56 (60.2%) had high WBC. Total of 21 (22.6%) had Charcot's Triad positive. 66 (71.0%) patients had high risk, 25 (26.9%) had intermittent risk and 2 (2.2%) had low risk.

In terms of identifying the predictive factors, ALP (crude odds ratio of 2.512 and p-value of 0.025), ALT (crude odds ratio of 2.256 and p value of 0.042 were found to be

predictive factors on univariate analysis but none were found to be predictive factors on multivariate analysis

Table 3.2: Sensitivity specificity, PPV and NPV of EUS in detecting choledocholithiasis

	Choledocholithiasis	No choledocholithiasis	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
EUS positive	89	15	95.7 (CI 89.4-98.8)	84.8 (CI 76.2-91.2)	85.6 (CI 78.7-90.5)	95.4 (CI 88.9-98.2)
EUS negative	4	84				

*CI denotes confidence interval
Positive likelihood ratio = 6.3161
Negative likelihood ratio = 0.0507
Pre-test Probability = 0.4844
Post-test Probability = 0.8558

***Table 3.3**: Sensitivity specificity, PPV and NPV of TAS in detecting choledocholithiasis*

	Choledocholithiasis	No choledocholithiasis	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
TAS positive	39	11	41.9 (CI 31.8-52.6)	88.9% (CI 81.0-94.3)	78% (CI 65.9-86.7)	62.0% (CI 57.5-66.2)
TAS negative	54	88				

*CI denotes confidence interval

Positive likelihood ratio = 3.7742
Negative likelihood ratio = 0.6532
Pre-test Probability = 0.4844
Post-test Probability = 0.78

Table 3.4: Sensitivity specificity, PPV and NPV of EUS in Low to Intermediate risk group (n=78)

	EUS Positive	EUS Negative	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Choledocholithiasis	24	3	70.59% (CI 52.52-84.9)	93.18% (CI 81.34-98.57)	88.89% (CI 72.43-96.06)	80.39% (CI 70.77-87.41)
No choledocholithiasis	10	41				

*CI denotes confidence interval

Positive likelihood ratio = 10.3529
Negative likelihood ratio = 0.3156
Pre-test Probability = 0.4359
Post-test Probability = 0.8889

Table 3.5: Sensitivity specificity, PPV and NPV of EUS in High risk group (n=114)

	EUS Positive	EUS Negative	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Choledocholithiasis	64	1	92.75% (CI 83.89-97.61)	97.73% (CI 87.98-99.94)	98.46% (CI 90.20-99.78)	89.58% (CI 78.69-95.24)
No Choledocholithiasis	5	43				

*CI denotes confidence interval

Positive likelihood ratio = 40.8116
Negative likelihood ratio = 0.0741
Pre-test Probability = 0.6106
Post-test Probability = 0.9846

Table 3.6: Predictive factors for choledocholithiasis

	Choledocholithiasis	Crude OR (95% CI)	P value	Adjusted OR (95% CI)[a]	P value
Age < 50 >50	 28(30.1%) 65(69.6%)	 1.270 (0.693, 2.325)	 0.439	-	-
Ethnicity Malays Chinese Indians Others (Non-Malay)	 39(41.9%) 37(39.8%) 16(17.2%) 1(1.1%)	 0.867 (0.490, 1.534)	 0.623	-	-
Gender Male Female	 48(51.6%) 45(48.4%)	 1.280 (0.726, 2.257)	 0.394	-	-
Abdominal pain Yes No	 81(87.1%) 12(12.9%)	 1.638 (0.729, 3.676)	 0.232	-	-
GGT Elevated Non elevated	 92(98.9%) 1(1.1%)	 2.875 (0.294, 28.141)	 0.364	-	-
ALP Elevated Non elevated	 83(89.2%) 10(10.8%)	 2.512 (1.123, 5.618)	 0.025	 2.206 (0.968, 5.028)	 0.060
AST Elevated Non elevated	 85 (91.4%) 8 (8.6%)	 2.048 (0.832, 5.043)	 0.119	-	-
ALT Elevated Non elevated	 82 (88.2%) 11 (11.8%)	 2.256 (1.031, 4.938)	 0.042	 1.943 (0.869, 4.344)	 0.106
WBC Elevated Non elevated	 56 (60.2%) 37 (39.8%)	 0.792 (0.440, 1.424)	 0.435	-	-
Amylase Elevated Non elevated	 42 (45.2%) 51 (54.8%)	 0.659 (0.373, 1.164)	 0.151	-	-

Note: [a] Backward LR was used for variable selection.

CHAPTER 4: DISCUSSION

The main aim of this study was to confirm the utility of EUS in suspected CBD stones as well as to audit our own EUS performance for this condition. From this study, we have confirmed that EUS is indeed very accurate and far superior to TAS. This is consistent with previous studies. (Prachayakul et al. 2014)

The study also provides further evidence that EUS is a very safe procedure with a low risk of complications as only 3 patients (0.2%) developed this in the past 5 years. On the other hand, ERCP was associated with about 3.5% risk of pancreatitis, 0.5% risk of perforation and 1% risk of sedation related complications such as respiratory depression and cardiopulmonary complications in other studies. (Committee et al. 2012). Moreover, the cost of EUS at present in our setting is approximately RM 280, compared to the cost of ERCP about RM 1700. Therefore, if we were to extrapolate the numbers and to solely use TAS for the diagnosis of choledocholithiasis, we would have missed 43 (46%) CBD stones. As previously mentioned, MRCP is not practical in our setting due to long waiting periods and high cost. EUS however, is available on every working day and can be carried out within 24 hours of presentation. In patients who are found to have choledocholithiasis on EUS, an ERCP is carried out in the same setting. The current ASGE guideline suggests high risks patients should proceed directly to ERCP (Committee et al. 2010). However, in our setting, almost half the patients in the high risk did NOT have choledocholithiasis. Therefore, we believe it is not an acceptable strategy to proceed straight to ERCP in a high-risk group as this will lead to a high number of unnecessary ERCPs. The likelihood of choledocholithiasis in the normal EUS is very low due to its high specificity. The specificity and sensitivity of EUS is even higher in this group (>90%) than overall.

Looking specifically at the predictive factors for choledocholithiasis, no significant association was found with any of the clinical and biochemical parameters. Multiple

studies previously also showed unreliability of clinical and biochemical parameters (Anderloni et al. 2014; Lee et al. 2008; Prachayakul et al. 2014; Jovanovic et al. 2011) This study clearly supports these findings, underlining the real-life challenge that physicians face in making a diagnosis of choledocholithiasis.

There were several limitations of the study. First of all, as it was a retrospective study, we had to exclude cases with missing data, which meant that a large number of patients were excluded. In addition, there were some patients with suspected choledocholithiasis who underwent ERCP immediately after TAS, therefore the overall true sensitivity of TAS in detecting choledocholithiasis is expected to be higher than what was calculated from the study. Moreover, TAS was conducted by multiple trainees and radiographers, who may be unsupervised. Whereas all the EUS cases are done either by an experienced endosonographer or a trainee with strict supervision. Hence, the study shows that TAS alone is insufficient to rule out choledocholithiasis.

In conclusion, this study has confirmed the invaluable role of EUS in the diagnosis of choledocholithiasis. The introduction of EUS in our Centre has resulted in a paradigm change in the diagnostic workup for this condition.

Despite the high accuracy of EUS, there is still room for improvement in our centre. All false positive and false negative cases should be reviewed to identify the potential causes. It is also clear that EUS should be an integral service in all endoscopy units throughout Malaysia. Methods to ensure this includes national clinical practice guidelines and training workshops. The national training program in gastroenterology and hepatology started in 2016 has already introduced EUS an integral part of the curriculum. To date, University Malaya Medical Centre had already conducted six workshops in EUS since 2012 and this should be ongoing.

CHAPTER 5: BIBLIOGRAPHY

(MGIR), The Malaysian Gastro-Intestinal Registry. 2009. 'Malaysian Gastro-Intestinal Registry 1st Report 2009'.

Anderloni, A., M. Ballare, M. Pagliarulo, D. Conte, M. Galeazzi, M. Orsello, S. Andorno, and M. Del Piano. 2014. 'Prospective evaluation of early endoscopic ultrasonography for triage in suspected choledocholithiasis: results from a large single centre series', *Dig Liver Dis*, 46: 335-9.

Committee, Asge Standards of Practice, M. A. Anderson, L. Fisher, R. Jain, J. A. Evans, V. Appalaneni, T. Ben-Menachem, B. D. Cash, G. A. Decker, D. S. Early, R. D. Fanelli, D. A. Fisher, N. Fukami, J. H. Hwang, S. O. Ikenberry, T. L. Jue, K. M. Khan, M. L. Krinsky, P. M. Malpas, J. T. Maple, R. N. Sharaf, A. K. Shergill, and J. A. Dominitz. 2012. 'Complications of ERCP', *Gastrointest Endosc*, 75: 467-73.

Committee, Asge Standards of Practice, J. T. Maple, T. Ben-Menachem, M. A. Anderson, V. Appalaneni, S. Banerjee, B. D. Cash, L. Fisher, M. E. Harrison, R. D. Fanelli, N. Fukami, S. O. Ikenberry, R. Jain, K. Khan, M. L. Krinsky, L. Strohmeyer, and J. A. Dominitz. 2010. 'The role of endoscopy in the evaluation of suspected choledocholithiasis', *Gastrointest Endosc*, 71: 1-9.

DiMagno, E. P., J. L. Buxton, P. T. Regan, R. R. Hattery, D. A. Wilson, J. R. Suarez, and P. S. Green. 1980. 'Ultrasonic endoscope', *Lancet*, 1: 629-31.

Dimagno, E. P., P. T. Regan, J. E. Clain, E. M. James, and J. L. Buxton. 1982. 'Human endoscopic ultrasonography', *Gastroenterology*, 83: 824-9.

Freeman, M. L. 2012. 'Complications of endoscopic retrograde cholangiopancreatography: avoidance and management', *Gastrointest Endosc Clin N Am*, 22: 567-86.

Jenssen, C., M. V. Alvarez-Sanchez, B. Napoleon, and S. Faiss. 2012. 'Diagnostic endoscopic ultrasonography: assessment of safety and prevention of complications', *World J Gastroenterol*, 18: 4659-76.

Jovanovic, P., N. N. Salkic, E. Zerem, and F. Ljuca. 2011. 'Biochemical and ultrasound parameters may help predict the need for therapeutic endoscopic retrograde cholangiopancreatography (ERCP) in patients with a firm clinical and biochemical suspicion for choledocholithiasis', *Eur J Intern Med*, 22: e110-4.

Lee, Y. T., F. K. Chan, W. K. Leung, H. L. Chan, J. C. Wu, M. Y. Yung, E. K. Ng, J. Y. Lau, and J. J. Sung. 2008. 'Comparison of EUS and ERCP in the investigation with suspected biliary obstruction caused by choledocholithiasis: a randomized study', *Gastrointest Endosc*, 67: 660-8.

Prachayakul, V., P. Aswakul, P. Bhunthumkomol, and M. Deesomsak. 2014. 'Diagnostic yield of endoscopic ultrasonography in patients with intermediate or high likelihood of choledocholithiasis: a retrospective study from one university-based endoscopy center', *BMC Gastroenterol*, 14: 165.

Sakijan, A. S., and M. Atan. 1987. 'Choledocholithiasis: diagnosis by ultrasound', *Med J Malaysia*, 42: 115-8.

Sugiyama, M., and Y. Atomi. 1997. 'Endoscopic ultrasonography for diagnosing choledocholithiasis: a prospective comparative study with ultrasonography and computed tomography', *Gastrointest Endosc*, 45: 143-6.

Tse, F., L. Liu, A. N. Barkun, D. Armstrong, and P. Moayyedi. 2008. 'EUS: a meta-analysis of test performance in suspected choledocholithiasis', *Gastrointest Endosc*, 67: 235-44.

Yaghoobi, M., Y. Meeralam, and K. Al-Shammari. 2017. 'Diagnostic accuracy of EUS compared with MRCP in detecting choledocholithiasis: a meta-analysis of diagnostic test accuracy of head-to-head studies', *Gastrointest Endosc*.