—Original Article—

EUS assessment for intermediate risk of choledocholithiasis after a negative magnetic resonance cholangiopancreatography

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ABSTRACT

Background and Objectives: Guidelines recommend either EUS or magnetic resonance cholangiopancreatography (MRCP) for intermediate risk of choledocholithiasis. There is a lack of evidence that supports proceeding with EUS if the MRCP is negative and if clinical suspicion still exists. **Methods:** This is a retrospective study of all patients who underwent EUS to assess for choledocholithiasis at a tertiary care referral center from July 2013 to October 2019. **Results:** A total of 593 patients underwent EUS for evaluation for choledocholithiasis. Of the 593 patients, 35.2% (209/593) had an MRCP. 73.2% (153/209) had a negative MRCP while 26.8% (56/209) had a positive MRCP. Of the group of patients who underwent EUS with a negative MRCP, 15% (23/153) were positive for choledocholithiasis on EUS. Of these, 91% (21/23) were also positive for sludge or stones on endoscopic retrograde cholangiopancreatography and thus 14% (21/153) of the EUS were "true positives." There were no clinical or laboratory factors predictive of choledocholithiasis on univariate analysis in the EUS plus negative MRCP group. When further analyzing the MRCP negative group into MRCP-/EUS+ and MRCP-/EUS-subgroups, a total bilirubin >3 mg/dL predicted a bile duct stone (55% *vs.* 32%, $P = 0.05$). **Conclusion:** The diagnostic yield of EUS for suspected choledocholithiasis in the setting of a negative MRCP is 14% in our cohort. EUS should be considered in patients with intermediate risk of choledocholithiasis with a negative MRCP if the clinical suspicion is still present, and especially if the total bilirubin is above 3 mg/dL.

Key words: choledocholithiasis, EUS, magnetic resonance cholangiopancreatography, stone

INTRODUCTION

Gallstone disease can affect up to 15% of the population in the United States and is one of the

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leading causes of hospital admissions.[1] The annual cost of gallstone disease is over 6.6 billion dollars.[2] Up to 20% of patients with cholelithiasis can develop choledocholithiasis.[3] According to the American Society of Gastrointestinal Endoscopy (ASGE) and European Society of Gastrointestinal Endoscopy (ESGE), those who have high-risk criteria for choledocholithiasis should proceed directly to ERCP.[4,5] These criteria include choledocholithiasis seen on imaging, an total bilirubin >4 mg/dL and with a dilated bile duct, and ascending cholangitis. Low risk for choledocholithiasis is the presence of normal liver function tests and normal abdominal ultrasound.[5] No further workup is needed for low-risk patients. Intermediate risk is defined as abnormal liver function tests or dilated bile duct on ultrasound.[4,5] In this scenario, it is recommended to undergo EUS or magnetic resonance cholangiopancreatography (MRCP) for further diagnostic evaluation.

In 2015, a Cochrane review compared the diagnostic accuracy of EUS to MRCP for suspected choledocholithiasis.[6] The comprehensive review concluded that both EUS and MRCP have high diagnostic accuracy for detection of common bile duct (CBD) stones and thus those who have a negative EUS or MRCP do not need further invasive workup. It does stipulate, however, that if symptoms persist, further investigation is indicated. In our clinical practice, we will occasionally consult on patients with intermediate risk for CBD stones with abdominal pain in the setting of a negative MRCP. In this situation we consider performing an EUS, and we have found positive results on EUS that then lead to therapeutic ERCP [Figure 1] and resolution of symptoms. However to our knowledge there is no literature on the yield of EUS when an MRCP is negative. This study aimed to evaluate the diagnostic yield of EUS in this clinical situation.

METHODS

This is a retrospective study of all patients who underwent EUS to assess for CBD stones at a tertiary care referral center from July 2013 to October 2019. All procedures were standard of care, in accordance with the ethical standards of the responsible committee on human experimentation, and with the Helsinki Declaration of 1975, as revised in 2000. Institutional review board approval was granted for this study. The primary aim of this study was to report our diagnostic yield for choledocholithiasis found by EUS in patients with intermediate risk of choledocholithiasis who underwent a negative MRCP and subsequent EUS for continued suspicion of a bile duct stone based on one of the following: Continued abdominal pain and/or abnormal Liver enzymes. Secondary outcomes were to determine if there were any clinical or laboratory predictors that would predict a positive EUS in the setting of a negative MRI.

Inclusion criteria included: (1) patients with intermediate risk for choledocholithiasis undergoing an EUS procedure with or without a prior MRI/MRCP. Intermediate risk was defined as per the ASGE guidelines as presence of a dilated bile duct >6 mm or a bilirubin 1.8 mg/dL - 4.0 in the absence of a stone seen on imaging, cholangitis, or a total bilirubin >4.0 mg/dL in patients with right upper quadrant (RUQ) pain or clinical gallstone pancreatitis[4] (2) age >18 years old. EUS data was abstracted from a prospectively maintained endoscopy database and clinical characteristics, laboratory values, and radiology reports were obtained from the corresponding electronic charts of patients who met inclusion criteria. Covariates of interest included demographic characteristics, lab parameters, and clinical parameters. Demographic characteristics included age (years) and gender (female, male). Lab parameters included white blood cell count ($<10.5 \times 10^9$/L, $\geq 10.5 \times 10^9$/L), aspartate

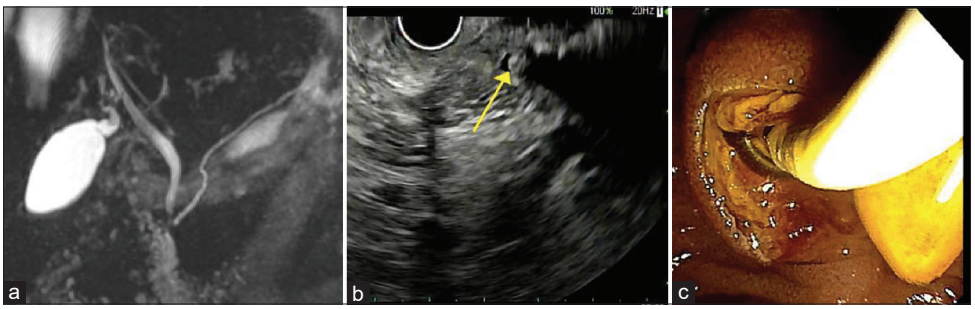

Figure 1. An example from a patient in this study showing (a) a negative magnetic resonance cholangiopancreatography (b) a subsequent EUS showing a bile duct stone (yellow arrow), and (c) a bile duct stone being removed on ERCP

aminotransferase (≤40 U/L, >40 U/L), alanine aminotransferase, (≤41 U/L, >40 U/L), alkaline phosphatase (≤120 U/L, >120 U/L), and total bilirubin (≤3 mg/dL, >3 mg/dL). Clinical parameters included RUQ pain (yes, no), fever (yes, no), acute pancreatitis (yes, no), and bacteremia (yes, no).

All EUS procedures were performed using a curved linear array echoendoscope (GF-UCT180, Olympus America, Center Valley, PA, USA) attached to an ultrasound system (Prosound F75 Processor, Hitachi Healthcare Americas, Twinsburg, OH, USA). If the EUS was positive for choledocholithiasis (round hyperechoic object with shadowing) it was then followed by an ERCP. The standard of care for choledocholithiasis in our health system, is to perform an ERCP regardless of the bile duct size; as intraoperative cholangiogram is not guaranteed to remove the stone. In addition, intra-operative cholangiogram is not routinely performed on every patient undergoing cholecystectomy, and is performed at the discretion of the surgeon. A "true positive" EUS was defined by a positive EUS plus a stone or obvious visible sludge removed on ERCP. Thus, ERCP was considered the gold standard for the diagnosis of choledocholithiasis. Stone size was not routinely measured on EUS or ERCP as it did not impact clinical decision-making or care. All patients that had a positive EUS and negative MRCP had the MRCP re-reviewed by an experienced gastrointestinal radiologist to confirm the MRCP was truly negative. This was done to mitigate the potential bias of a false negative MRCP that can occur due to the inherently imperfect interobserver agreement of radiology studies.[7,8]

For data analysis, patients included in the study were stratified into three subgroups: EUS plus no MRCP, EUS plus negative MRCP, and EUS plus positive MRCP (EUS performed just prior to ERCP to confirm the stone was still present in the bile duct and did not pass). Baseline characteristics, lab parameters, and clinical parameters were described for the entire study population and compared across subgroups. The continuous variables were described using means and standard deviations or medians and interquartile ranges. Categorical variables were described using frequencies and percentages. Significant differences between subgroups were evaluated with the Chi-square test, Fisher's exact test, one-way ANOVA test, or two-sample *t*-test, as appropriate. A log transformation was used to normalize the distribution of time from MRCP to EUS/ERCP prior to analysis.

The MRCP performed and negative subgroup was further stratified into EUS positive and EUS negative. Demographic characteristics, lab parameters, and clinical parameters were compared between MRCP−/EUS+ and MRCP−/EUS− subgroups as well as between MRCP−/EUS+ and no MRCP. The continuous variable was summarized using mean and standard deviation, and a two-sample *t*-test was used to test for a significant difference across subgroups. Categorical variables were summarized using frequency and percent, and the Chi-square test or Fisher's exact test was used to test for any significant differences across MRCP groups, as appropriate.

For each subgroup, univariable analysis for bivariate associations between each covariate and choledocholithiasis (diagnosed by gold standard ERCP) was performed using logistic regression. For the subgroup "EUS plus no MRCP," there were sufficient patients to conduct a multivariable analysis to determine the independent effect of covariates using multivariable logistic regression. Variables were included in the multivariable regression if they were found to have a significant univariable association. A relaxed $P < 0.10$ was used for inclusion in the multivariable model to avoid excluding important variables. For the subgroups "EUS plus negative MRCP" and "EUS plus positive MRCP" there were insufficient patients to conduct multivariable analyses.

Sensitivity analyses were performed to assess the importance of missing lab parameter data. The first sensitivity analysis was conducted by substituting a "normal" lab value range for all participants with missing data, and the second sensitivity analysis was conducted by substituting an "non-normal" lab value for all participants with missing data. Both sensitivity analyses included 573 patients. All analyses were performed using SAS Studio version 3.8, SAS, Cary, North Carolina, USA with $P < 0.05$ considered significant unless otherwise noted.

RESULTS

A total of 593 patients underwent an EUS to evaluate for choledocholithiasis. Figure 2 is a flowchart of patients included in this study. Of the 593 patients, 64.7% (384/593) did not have an MRCP. In this subgroup "EUS plus no MRCP," 34% (132/384) had an EUS positive for choledocholithiasis of which 97% (128/132) was confirmed on ERCP. Thus, 33% (128/384) of these patients had a "true

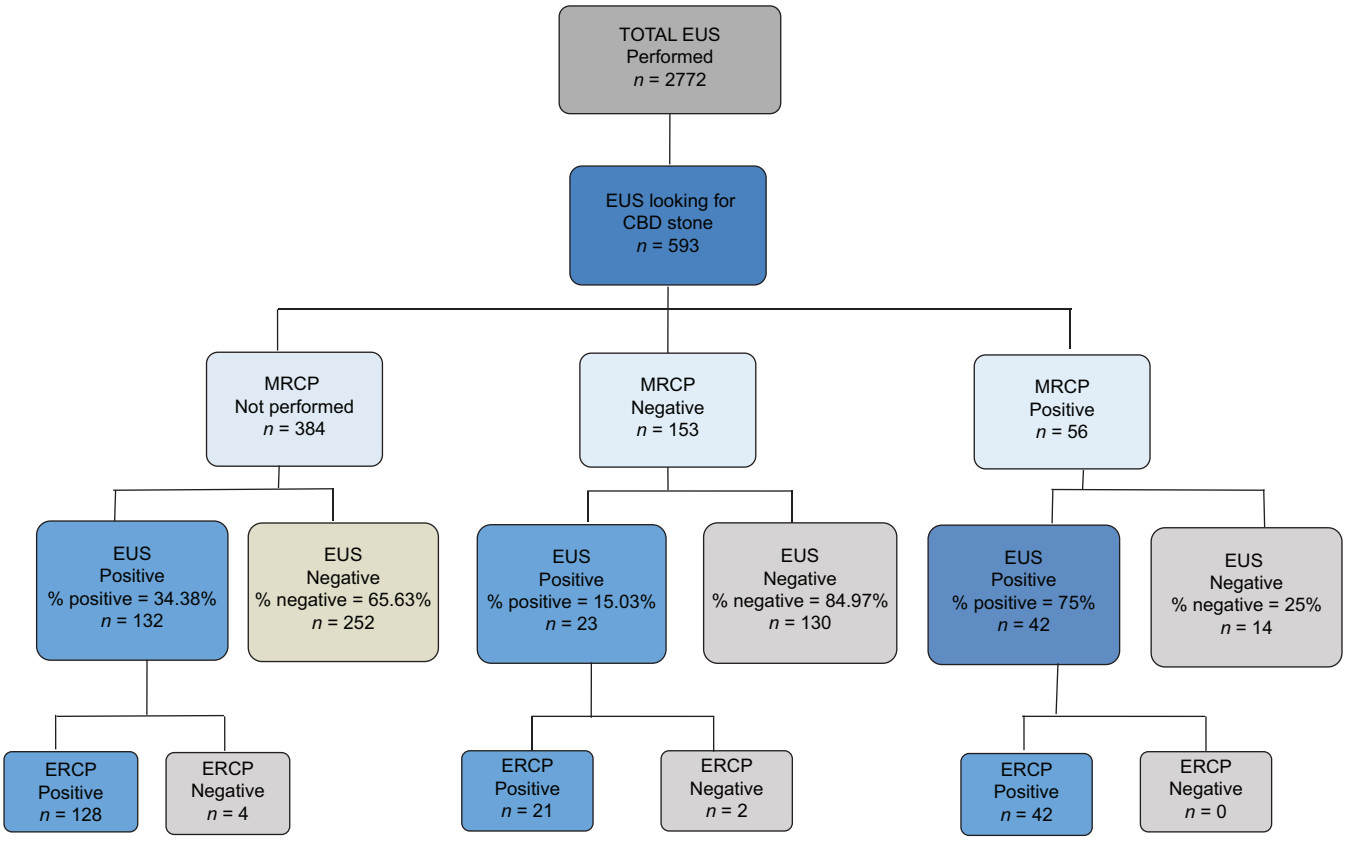

Figure 2. A flowchart of patients included in this study. MRCP: magnetic resonance cholangiopancreatography

positive" EUS. 35.2% of the patients (209/593) had a MRCP; 73.2% (153/209) had a negative MRCP while 26.8% (56/209) had a positive MRCP. Of the patients in the subgroup "EUS plus negative MRCP," 15% (23/153) had a EUS positive for choledocholithiasis while 85% (130/153) had a negative EUS. Of the patients with positive EUS in this subgroup, 91% (21/23) were confirmed positive on ERCP and thus 14% (21/153) had a "true positive" EUS. The 56 patients in the subgroup "EUS plus positive MRCP" had an EUS performed to confirm choledocholithiasis prior to ERCP. Of these patients, 75% (42/56) were positive for a stone on EUS. The ERCP that followed was positive for a stone in all 42 cases (75% (42/56) "true positive" EUS rate). The patients that tested negative for a stone on EUS (25%, 14/56) did not undergo subsequent ERCP.

Of the 593 patients analyzed for the primary outcome, 503 patients could be analyzed for the secondary outcome; to discover clinical or laboratory predictors that predict a "true positive" EUS in the setting of a negative MRCP. 90 patients were not included because they had missing data for at least one clinical or laboratory parameter. Table 1 shows the clinical and laboratory data in each of the three subgroups.

Table 2 shows the main secondary outcome of interest, the univariate analysis evaluating whether there are any clinical or laboratory parameters that predict a "true positive" EUS for choledocholithiasis in patients that had a negative MRCP. We show here that there are no statistically significant associations that predict choledocholithiasis in this group. When further analyzing the MRCP negative group into MRCP−/EUS+ and MRCP−/EUS− subgroups, a total bilirubin >3 mg/dL predicted a bile duct stone [Table 3].

Among patients who did not have a MRCP and went straight to EUS+/−ERCP, univariate and multivariate analysis [Table 4] showed that alkaline phosphatase >120 U/L (odds ratio [OR] 2.39 $P = 0.0065$), RUQ pain (OR 3.22, $P = 0.0008$), and acute pancreatitis (OR 0.5, $P = 0.028$) all predict choledocholithiasis found on both EUS and ERCP.

There were 21 patients who had negative MRCPs but had "true positive" EUS. These MRCPs were re-reviewed by a senior GI radiologist. Both radial

Table 1. Differences in demographic characteristics, lab parameters, and clinical parameters across subgroups

	EUS plus no MRCP (*n*=328), *n* (%)	EUS plus negative MRCP (*n*=124), *n* (%)	EUS plus positive MRCP (*n*=54), *n* (%)	*P*
Baseline characteristics				
Age (years), mean (SD)	54.45 (18.77)	52.77 (18.17)	54.59 (21.62)	0.68
Gender				
Female	207 (63.11)	76 (61.29)	44 (81.48)	0.02
Male	121 (36.89)	48 (38.71)	10 (18.52)	
Cholecystectomy status				
No	254 (77.44)	85 (68.55)	45 (83.33)	0.06
Yes	74 (22.56)	39 (31.45)	9 (16.67)	
Lab parameters				
WBC				
<10.5×10^9/L	236 (71.95)	96 (77.42)	44 (81.48)	0.22
≥10.5×10^9/L	92 (28.05)	28 (22.58)	10 (18.52)	
AST				
≤40 U/L	108 (32.93)	34 (27.42)	15 (27.78)	0.46
>40 U/L	220 (67.07)	90 (72.58)	39 (72.22)	
ALT				
≤41 U/L	94 (28.66)	35 (28.23)	13 (24.07)	0.79
>41 U/L	234 (71.34)	89 (71.77)	41 (75.93)	
Alkaline phosphatase				
≤120 U/L	139 (42.38)	38 (30.65)	15 (27.78)	0.02
>120 U/L	189 (57.62)	86 (69.35)	39 (72.22)	
Total bilirubin				
≤3 mg/dL	241 (73.48)	80 (64.52)	41 (75.93)	0.13
>3 mg/dL	87 (26.52)	44 (35.48)	13 (24.07)	
Clinical parameters				
RUQ pain				
No	79 (24.09)	39 (31.45)	14 (25.93)	0.28
Yes	249 (75.91)	85 (68.55)	40 (74.07)	
Fever				
No	294 (89.63)	106 (85.48)	51 (94.44)	0.19
Yes	34 (10.37)	18 (14.52)	3 (5.56)	
Acute pancreatitis				
No	248 (75.61)	101 (81.45)	50 (92.59)	0.013
Yes	80 (24.39)	23 (18.55)	4 (7.41)	
Bacteremia				
No	317 (96.65)	120 (96.77)	52 (96.30)	1.00
Yes	11 (3.35)	4 (3.23)	2 (3.70)	
Time from MRCP to EUS/ERCP (h)				
Median (Q1–Q3)	NA	54.92 (25.82–217.23)	54.06 (26.38–163.28)	0.9973

OR: Odds ratio; CI: Confidence interval; WBC: White blood cell count; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; RUQ: Right upper quadrant; MRCP: Magnetic resonance cholangiopancreatography

MRCP and 3D respiratory-triggered images were reviewed. Of the MRCP studies, 90% (19/21) were determined to be negative for choledocholithiasis. The bile duct size was measured in these cases and the median bile duct size was 7 mm with a range of 5–14 mm.

DISCUSSION

To our knowledge, this is the first study to examine the diagnostic yield of EUS when the MRCP is negative for choledocholithiasis. A few studies studies have showed the benefit of EUS after a negative computed tomography (CT) scan. In a study of 156 patients, EUS showed a 34% (53/156) yield when the CT scan was negative.[9] Another study showed a 28% yield of choledocholithiasis in 72 patients whose CT scans were negative. The sensitivity and specificity for choledocholithiasis in this cohort was 87% and 100% respectively.[10] A third study retrospectively evaluated 200 patients with intermediate or high probability for choledocholithiasis and negative CT scans.[11] EUS

Table 2. Univariable association between covariates and "true positive" EUS for choledocholithiasis among those with negative magnetic resonance cholangiopancreatography (*n*=124)

Variable	Univariable OR (95% CI)	*P*
Age	1.00 (0.97-1.03)	0.9238
Sex (male *vs.* female)	1.01 (0.36-2.81)	0.9865
WBC (≥10.5×10⁹/L *vs.* <10.5×10⁹/L)	0.17 (0.02-1.36)	0.0947
AST (>40 U/L *vs.* ≤40 U/L)	0.98 (0.32-2.99)	0.9705
ALT (>41 U/L *vs.* ≤41)	1.03 (0.34-3.13)	0.9637
Alkaline phosphatase (>120 U/L *vs.* ≤120 U/L)	2.47 (0.67-9.08)	0.1751
Total bilirubin (>3 mg/dL *vs.* ≤3 mg/dL)	2.03 (0.74-5.56)	0.1693
RUQ pain (yes *vs.* no)	2.57 (0.70-9.46)	0.1555
Fever (yes *vs.* no)	0.31 (0.04-2.47)	0.2676
Acute pancreatitis (yes *vs.* no)	0.51 (0.11-2.37)	0.3876
Bacteremia (yes *vs.* no)	0.62 (0.02-16.76)	0.7737

*Firth logistic regression used to address quasi-complete separation of data. OR: Odds ratio; CI: Confidence interval; WBC: White blood cell count; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; RUQ: Right upper quadrant

Table 3. Differences in demographic characteristics, lab parameters, and clinical parameters between magnetic resonance cholangiopancreatography−/EUS+ and magnetic resonance cholangiopancreatography−/EUS− subgroups (*n*=124)

	MRCP-/EUS+ (*n*=18), *n* (%)	MRCP-/EUS- (*n*=106), *n* (%)	*P*
Demographic characteristics			
Age, mean (SD)	54.17 (16.71)	52.53 (18.47)	0.73
Sex			
Female	11 (61.11)	65 (61.32)	0.99
Male	7 (38.89)	41 (38.68)	
Lab parameters			
WBC			
<10.5×10⁹/L	17 (94.44)	79 (74.53)	0.07
≥10.5×10⁹/L	1 (5.56)	27 (25.47)	
AST			
≤40 U/L	5 (27.78)	29 (27.36)	1.00
>40 U/L	13 (72.22)	77 (72.64)	
ALT			
≤41 U/L	5 (27.78)	30 (28.30)	0.96
>41 U/L	13 (72.22)	76 (71.70)	
Alkaline phosphatase			
≤120 U/L	3 (16.67)	35 (33.02)	0.16
>120 U/L	15 (83.33)	71 (66.98)	
Total bilirubin			
≤3 mg/dL	8 (44.44)	72 (67.92)	0.05
>3 mg/dL	10 (55.56)	34 (32.08)	
Clinical parameters			
RUQ pain			
No	3 (16.67)	36 (33.96)	0.14
Yes	15 (83.33)	70 (66.04)	
Fever			
No	17 (94.44)	89 (83.96)	0.47
Yes	1 (5.56)	17 (16.04)	
Acute pancreatitis			
No	16 (88.89)	85 (80.19)	0.52
Yes	2 (11.11)	21 (19.81)	
Bacteremia			
No	18 (100.00)	102 (96.23)	1.00
Yes	0 (0.00)	4 (3.77)	

OR: Odds ratio; CI: Confidence interval; WBC: White blood cell count; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; RUQ: Right upper quadrant; SD: Standard deviation

diagnosed a stone in 165/200 patients (83%) and 161 (81%) were confirmed on ERCP. EUS had an accuracy of 94%, sensitivity of 98% and a specificity of 80%. Thus, similar to our article EUS does have a small amount of false negatives and may result in unnecessary ERCP; two in our series and four in the aforementioned study. It should be noted that the ASGE and ESGE guidelines recommend an EUS or MRCP for evaluation of patients with intermediate risk of choledocholithiasis after a negative transabdominal ultrasound, and not a CT scan.[4,5]

Transabdominal ultrasound is not sensitive for choledocholithiasis with reports ranging from 22% to 55%.[12] However, transabdominal ultrasound is recommended for workup of choledocholithiasis as it is a quick exam and it does detect bile duct dilation in 77-87% of the time.[12] EUS on the other hand has reported sensitivities from 75% to 100% with sensitivities of 85%–100%.[6] For MRCP the sensitivities range from 77% to 100% with specificities from 73% to 99%. In a meta-analysis of 5 head-to-head studies comparing EUS to MRCP for choledocholithiasis, the pooled sensitivity of EUS was 97% and 90% respectively *versus* 87% and 92% for MRCP respectively.[13] The diagnostic odds ratio was higher for EUS *versus* MRCP (163 *vs.* 79; $P = 0.008$) and was attributed to the higher sensitivity of EUS *versus* MRCP ($P = 0.006$). The meta-analysis concluded that EUS should be in the diagnostic algorithm for choledocholithiasis when possible. However, MRCP is less invasive, and does not require anesthesia. Thus, for patients with comorbidities, it may be a better choice.

Overall, this study shows that patients who are at intermediate risk for choledocholithiasis that undergo a negative MRCP may still be at risk for choledocholithiasis. Thus, if the clinical suspicion remains, an EUS exam may be warranted, especially if the total bilirubin is above 3 mg/dL. In this study,

Table 4. Univariable and multivariable association between covariates and "true positive" EUS for choledocholithiasis among those no magnetic resonance cholangiopancreatography (*n*=328)

Variable	Univariable OR (95% CI)	*P**	Multivariable OR (95% CI)	*P*
Age	1.01 (1.00-1.02)	0.0928	1.02 (1.00-1.03)	0.01
Sex (male *vs.* female)	0.73 (0.45-1.17)	0.1880	-	-
WBC (≥10.5×10^9/L *vs.* <10.5×10^9/L)	1.29 (0.78-2.11)	0.3181	-	-
AST (>40 U/L *vs.* ≤40 U/L)	3.27 (1.89-5.64)	<0.0001	1.22 (0.48-3.10)	0.68
ALT (>41 U/L *vs.* ≤41 U/L)	3.77 (2.07-6.84)	<0.0001	1.64 (0.64-4.21)	0.31
Alkaline phosphatase (>120 U/L *vs.* ≤120 U/L)	3.85 (2.32-6.40)	<0.0001	2.39 (1.28-4.47)	0.006
Total bilirubin (>3 mg/dL *vs.* ≤3 mg/dL)	2.31 (1.40-3.81)	0.0011	1.36 (0.76-2.42)	0.30
RUQ pain (yes *vs.* no)	2.73 (1.49-5.00)	0.0011	3.22 (1.62-6.37)	0.0008
Fever (yes *vs.* no)	1.28 (0.62-2.64)	0.5053	-	-
Acute pancreatitis (yes *vs.* no)	0.55 (0.32-0.97)	0.0387	0.50 (0.27-0.93)	0.03
Bacteremia (yes *vs.* no)	1.50 (0.45-5.04)	0.5079	-	-

*A *P*<0.10 was used as a cutoff for selection into the multivariable model. OR: Odds ratio; CI: Confidence interval; WBC: White blood cell count; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; RUQ: Right upper quadrant

the MRCP exam missed a bile duct stone 14% of the time compared to the gold standard ERCP. It is important to note that our study is not showing a superiority of EUS to MRCP, as such a study would be designed differently. However, it does show that EUS can be a useful tool to determine if MRCP missed a stone. While a 14% diagnostic yield of EUS could be considered moderate, it is important to note that MRCP is considered a very sensitive test, and thus one can argue that a 14% increased yield for diagnosis of choledocholithiasis in an intermediate risk group is significant. Moreover, 14% of undiagnosed bile duct stones can lead to clinically significant illness caused by acute pancreatitis or acute cholangitis in a population with symptomatic choledocholithiasis.

We examined clinical and laboratory variables that could be predictive of choledocholithiasis on both EUS and subsequent ERCP. It was found that there were no variables that predicted choledocholithiasis in the negative MRCP group. When further analyzing the MRCP negative group into MRCP−/EUS+ and MRCP−/EUS− subgroups, a total bilirubin >3 mg/dL predicted a bile duct stone. Generally, a total bilirubin around 3 mg/dL does not predict bile duct stones, and thus a high-risk cohort for choledocholithiasis is defined as 4 mg/dL or above.[4] However in this subgroup of the study, a lower bilirubin was statistically the cut off.

In the group that had no MRCP, the following abnormal results predicted choledocholithiasis: RUQ pain, abnormal alkaline phosphatase, and acute pancreatitis. This intuitively makes clinical sense, as these patients would be considered to have a higher suspicion for choledocholithiasis based on these abnormal findings and thus would proceed directly to EUS+/−ERCP.

In order to estimate the percentage of human error in this study, all patients with negative MRCPs but had "true positive" EUS had the MRCP re-read by an experienced GI radiologist. Two of these 21 negative MRCPs were in fact positive on the re-read. This shows that interobserver variability does play a small role in MRCP readings and should be taken into account in clinical care. Perhaps all patients with negative MRCPs that still have a high clinical suspicion for choledocholithiasis should have the MRCP re-reviewed with a senior radiologist if available.

There are limitations to our study. First, this is a retrospective study that can have its inherent associated limitations. However, we attempted to mitigate this with a re-review of MRCP images from an experienced radiologist. In addition, the gold standard for a diagnosis of choledocholithiasis was an objective ERCP finding of visible sludge or stones, not solely based on the positive EUS interpretation that can be subjective. It should be noted that it is possible that the stone seen on EUS had migrated into the bile duct form the gallbladder after the MRCP was performed; given the EUS was performed after the MRCP and not at the same time of the MRCP. However it should be noted that these patients had continued pain and suspected bile duct stones, so this is unlikely. Furthermore, of the 593 patients, 90 could not be evaluated for secondary outcomes due to missing lab or clinical data. However, this did not affect the primary outcome and thus we feel does not hinder the study in a major way. Finally, this study was conducted in a tertiary care center with experienced endosonographers specifically trained in

advanced endoscopy. Thus the results of this study are limited to expert centers.

CONCLUSION

We show that EUS can be a helpful tool that may aid in the diagnosis of choledocholithiasis when an MRCP is negative. The increased diagnostic yield of EUS found in this study contributes to the data from previous head-to-head studies showing the superiority of EUS to MRCP for the diagnosis of choledocholithiasis. Thus, EUS should be considered the favored choice in the diagnostic algorithm for choledocholithiasis if patients have limited comorbidities and can tolerate anesthesia.

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Conflicts of interest
There are no conflicts of interest.

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