

## Retrospective Study

**Endoscopic retrograde cholangiopancreatography for suspected choledocholithiasis: From guidelines to clinical practice**

Joana Magalhães, Bruno Rosa, José Cotter

Joana Magalhães, Bruno Rosa, José Cotter, Gastroenterology Department, Centro Hospitalar do Alto Ave, 4835-044 Guimarães, Portugal

José Cotter, Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, 4710-057 Braga, Guimarães, Portugal

José Cotter, ICVS/3B's, PT Government Associate Laboratory, 4710-057 Braga, Guimarães, Portugal

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**Correspondence to:** Joana Magalhães, MD, Gastroenterology Department, Centro Hospitalar do Alto Ave, Rua dos Cutileiros, Creixomil, 4835-044 Guimarães, Portugal. [jmagalhaes@chaa.min-saude.pt](mailto:jmagalhaes@chaa.min-saude.pt)  
Telephone: +351-253-540330  
Fax: +351-253-421308

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**Abstract**

**AIM:** To study the practical applicability of the American Society for Gastrointestinal Endoscopy guidelines in suspected cases of choledocholithiasis.

**METHODS:** This was a retrospective single center study, covering a 4-year period, from January 2010 to December 2013. All patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) for suspected choledocholithiasis were included. Based on the presence or absence of predictors of choledocholithiasis (clinical ascending cholangitis, common bile duct (CBD) stones on ultrasonography (US), total bilirubin > 4 mg/dL, dilated CBD on US, total bilirubin 1.8-4 mg/dL, abnormal liver function test, age > 55 years and gallstone pancreatitis), patients were stratified in low, intermediate or high risk for choledocholithiasis. For each predictor and risk group we used the  $\chi^2$  to evaluate the statistical associations with the presence of choledocholithiasis at ERCP. Statistical analysis was performed using SPSS version 21.0. A *P* value of less than 0.05 was considered statistically significant.

**RESULTS:** A total of 268 ERCPs were performed for suspected choledocholithiasis. Except for gallstone pancreatitis (*P* = 0.063), all other predictors of cho-

ledocholithiasis (clinical ascending cholangitis,  $P = 0.001$ ; CBD stones on US,  $P \leq 0.001$ ; total bilirubin  $> 4$  mg/dL,  $P = 0.035$ ; total bilirubin 1.8-4 mg/dL,  $P = 0.001$ ; dilated CBD on US,  $P \leq 0.001$ ; abnormal liver function test,  $P = 0.012$ ; age  $> 55$  years,  $P = 0.002$ ) showed a statistically significant association with the presence of choledocholithiasis at ERCP. Approximately four fifths of patients in the high risk group (79.8%, 154/193 patients) had confirmed choledocholithiasis on ERCP, vs 34.2% (25/73 patients) and 0 (0/2 patients) in the intermediate and low risk groups, respectively. The definition of "high risk group" had a sensitivity of 86%, positive predictive value 79.8% and specificity 56.2% for the presence of choledocholithiasis at ERCP.

**CONCLUSION:** The guidelines should be considered to optimize patients' selection for ERCP. For high risk patients specificity is still low, meaning that some patients perform ERCP unnecessarily.

**Key words:** Choledocholithiasis; Endoscopic retrograde cholangiopancreatography; Cholangitis; Common bile duct stones; Dilated common bile duct

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**Core tip:** The American Society for Gastrointestinal Endoscopy (ASGE) proposes a stratification of patients according to the risk for choledocholithiasis, influencing subsequent management. Our study shown that the risk stratification, according to ASGE guidelines, may improve risk estimation of choledocholithiasis and should be considered to optimize patients' selection for endoscopic retrograde cholangiopancreatography (ERCP). However, even in the "high risk group" the specificity was low. Thus, at this point, it seems advisable that also "high risk" patients undergo further testing before being submitted to ERCP, similarly to those patients with "intermediate risk", while for patients with "low-risk" of choledocholithiasis a watchful waiting strategy seems adequate.

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## INTRODUCTION

Choledocholithiasis is the most common cause of biliary obstruction. Approximately 5% to 22% of the Western population has gallstones<sup>[1]</sup> and common bile duct stones occur in 8%-20%<sup>[2,3]</sup> of those patients. Patients suspected of having choledocholithiasis are

diagnosed with a combination of laboratory tests and imaging studies<sup>[4]</sup>. The first imaging study obtained is typically a transabdominal ultrasonography (US). When the ultrasound findings are not enough for a diagnosis a magnetic resonance cholangiopancreatography (MRCP) or an endoscopic ultrasound (EUS) should be considered.

The diagnosis of choledocholithiasis usually should be followed by some therapeutic intervention to remove the stones<sup>[4-7]</sup>. Endoscopic retrograde cholangiopancreatography (ERCP) is the standard method for the diagnosis and therapy of bile duct stones, however it is an invasive procedure not free of complications<sup>[8-11]</sup>.

According to the results of laboratory tests and US, the American Society for Gastrointestinal Endoscopy (ASGE) proposes to stratify a patient in low, intermediate or high risk for choledocholithiasis. Subsequent management will vary depending on the patient's level of risk<sup>[12]</sup>. The purpose of this study was to evaluate the practical applicability of the American Society for Gastrointestinal Endoscopy guidelines in a population of patients undergoing ERCP for suspected choledocholithiasis.

## MATERIALS AND METHODS

### Patients

We performed a retrospective single center study, covering a 4-year period, from January 2010 to December 2013. Patients referred for ERCP for suspected bile duct lithiasis were consecutively included. Patients presenting for stent exchange or follow-up of known and incompletely removed stones on previous ERCP were excluded.

Clinical data recorded from disease onset (age, gender, symptoms at presentation, laboratorial values) to the time of the ERCP (therapeutic procedures and related complications) were collected.

### Predictors of choledocholithiasis

According to ASGE guidelines<sup>[12]</sup>, cholangitis, total bilirubin  $> 4$  mg/dL and common bile duct (CBD) stone on US were considered very strong predictors. Total bilirubin 1.8-4 mg/dL and dilated CBD on US were considered strong predictors and abnormal liver biochemical tests, age  $> 55$  years and gallstone pancreatitis were considered moderate predictors. Patients with strong predictors or any very strong predictor were considered at high risk for choledocholithiasis. Patients without any predictor and all other patients were considered low and intermediate risk for choledocholithiasis, respectively. The diagnosis of cholangitis was established by the presence of Charcot's triad (fever, abdominal pain and jaundice). The diagnosis of CBD stone on US was considered when an intraductal echogenic focus with distal acoustic

**Table 1** Baseline characteristics of the study population *n* (%)

| Variable                       | Total ( <i>n</i> = 268) |
|--------------------------------|-------------------------|
| Gender, female                 | 161 (60.1)              |
| Age, mean ± SD                 | 66.8 ± 16.8             |
| Very strong predictors         |                         |
| Clinical ascending cholangitis | 36 (13.4)               |
| Common bile duct stone on US   | 109 (40.7)              |
| Total bilirubin > 4 mg/dL      | 102 (38.1)              |
| Strong predictors              |                         |
| Total bilirubin 1.8-4 mg/dL    | 84 (31.3)               |
| Dilated common bile duct on US | 195 (72.8)              |
| Moderate predictors            |                         |
| Abnormal liver function test   | 231 (86.2)              |
| Age > 55 yr                    | 197 (73.5)              |
| Gallstone pancreatitis         | 63 (23.5)               |

US: Ultrasonography.

shadow was identified. Dilated CBD on US was considered when bile duct diameter was > 6 mm in a patient without cholecystectomy. Abnormal liver biochemical tests were considered when aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (AP) presented elevated laboratory values, considering the reference lab values in our institution. Gallstone pancreatitis was considered when patients presented with abdominal pain (epigastric pain often radiating to the back), lipase (or amylase activity) at least 3 times higher than the upper limit of normal, stones or biliary sludge within gallbladder and no history of alcohol abuse.

### Endoscopic retrograde cholangiopancreatography procedure

Every ERCP was performed using Olympus® TJF 160 VR or TJF 145 side-viewing endoscopes. All patients provided written consent to undergo ERCP and were informed of the risks and benefits of the procedure. Patients were under propofol sedation assisted by an anaesthesiologist. Stone size and number were documented on the initial diagnostic cholangiogram at ERCP. Endoscopic sphincterotomy was performed over a guide wire. Some patients underwent papillary balloon dilation using a through-the-scope balloon catheter for oesophageal/pyloric dilation, gradually inflated to 12-18 mm according to the size of the largest stone and the maximal diameter of the distal bile duct on the cholangiogram. Stones were removed using a retrieval balloon catheter and/or a Dormia basket. When necessary, mechanical lithotripsy was performed to fragment the stones prior to removal. Complete clearance of the bile duct was documented with a balloon catheter cholangiogram at the end of the procedure. In the case of residual lithiasis, a biliary 7 Fr double pigtail plastic stent was placed and a second ERCP was planned within 10-12 wk. At the end of each ERCP, 100 mg rectal indomethacin was routinely given, to prevent post-ERCP pancreatitis. Prophylactic antibiotics were not routinely administered.

### Statistical analysis

Statistical analysis was performed using SPSS version 21.0 (SPSS® Inc., Chicago, IL, United States).

Quantitative data were described as mean ± SD and qualitative data as proportions. For each predictor and risk group the  $\chi^2$  was used to assess differences between presence vs absence of choledocholithiasis on ERCP. A *P* value < 0.05 was considered statistically significant.

For each risk group and their predictors the sensitivity, specificity, positive predictive values (PPV) and negative predictive value (NPV) were assessed.

## RESULTS

From January 2010 to December 2013, a total of 268 patients were referred for ERCP for suspected choledocholithiasis. Patients included in our study were predominantly female (60.1%), with a mean age of 66.8 ± 16.8 years. Choledocholithiasis was present in 179 ERCPs (66.8%). The predictors more often seen in our patients were the presence of abnormal liver biochemical tests (86.2%), age > 55 years (73.5%) and dilated CBD on US (72.8%). Main clinical features of the study population are shown in Table 1.

### Predictors of choledocholithiasis

Except for gallstone pancreatitis (*P* = 0.063), all other predictors showed a statistically significant difference between presence vs absence of choledocholithiasis on ERCP (cholangitis, *P* = 0.001; CBD stone on US, *P* < 0.001; total bilirubin > 4 mg/dL, *P* = 0.035; total bilirubin 1.8-4 mg/dL, *P* = 0.001; dilated CBD on US, *P* < 0.001; abnormal liver function test, *P* = 0.012; age > 55 years, *P* = 0.002) (Table 2).

The risk of choledocholithiasis, as shown by *odds ratio*, was increased for patients who presented with cholangitis (OR: 6.48, 95%CI: 1.93-21.80), common bile duct stone on US (OR: 11.25, 95%CI: 5.32-23.81), total bilirubin > 4 mg/dL (OR: 1.79, 95%CI: 1.04-3.08), total bilirubin 1.8-4 mg/dL (OR: 3.15, 95%CI: 1.63-6.08), dilated common bile duct on US (OR: 5.06, 95%CI: 2.85-8.99), abnormal liver function test (OR: 2.43, 95%CI: 1.20-4.90) and age > 55 years (OR: 2.37, 95%CI: 1.36-4.15) (Table 2).

### Risk group for choledocholithiasis

Of the 268 patients included in this study, 72% were stratified into the high risk group. Of the remaining patients, 27.2% and 0.8% were stratified into the intermediate and low risk groups, respectively. Approximately four fifths of patients in the high risk group (79.8%, 154/193 patients) had confirmed choledocholithiasis on ERCP. The presence of choledocholithiasis was identified in 34.2% (25/73) of intermediate risk patients. Any patient into the low risk group had choledocholithiasis on ERCP. There was a statistically significant association between

**Table 2 Predictors of choledocholithiasis - univariate analysis *n* (%)**

| Variable                       | Choledocholithiasis on ERCP | No Choledocholithiasis on ERCP | OR    | 95%CI      | <i>P</i> value |
|--------------------------------|-----------------------------|--------------------------------|-------|------------|----------------|
| Very strong predictors         |                             |                                |       |            |                |
| Clinical ascending cholangitis | 33 (91.7)                   | 3 (8.3)                        | 6.48  | 1.93-21.80 | 0.001          |
| Common bile duct stone on US   | 100 (91.7)                  | 9 (8.3)                        | 11.25 | 5.32-23.81 | < 0.001        |
| Total bilirubin > 4 mg/dL      | 76 (74.5)                   | 26 (25.5)                      | 1.79  | 1.04-3.08  | 0.035          |
| Strong predictors              |                             |                                |       |            |                |
| Total bilirubin 1.8-4 mg/dL    | 63 (75.0)                   | 21 (25.0)                      | 3.15  | 1.63-6.08  | 0.001          |
| Dilated common bile duct on US | 150 (76.9)                  | 45 (23.1)                      | 5.06  | 2.85-8.99  | < 0.001        |
| Moderate predictors            |                             |                                |       |            |                |
| Abnormal liver function test   | 161 (69.7)                  | 70 (30.3)                      | 2.43  | 1.20-4.90  | 0.012          |
| Age > 55 yr                    | 142 (72.1)                  | 55 (27.9)                      | 2.37  | 1.36-4.15  | 0.002          |
| Gallstone pancreatitis         | 36 (57.2)                   | 27 (42.8)                      | 0.58  | 0.32-1.03  | 0.063          |

ERCP: Endoscopic retrograde cholangiopancreatography; US: Ultrasonography.

**Table 3 Risk group for choledocholithiasis - univariate analysis *n* (%)**

| Variable                | Total      | Choledocholithiasis on ERCP | No Choledocholithiasis on ERCP | <i>P</i> value |
|-------------------------|------------|-----------------------------|--------------------------------|----------------|
| High risk group         | 193 (72.0) | 154 (79.8)                  | 39 (20.2)                      | < 0.001        |
| Intermediate risk group | 73 (27.2)  | 25 (34.2)                   | 48 (65.8)                      |                |
| Low risk group          | 2 (0.8)    | 0 (0)                       | 2 (100)                        |                |
| Very strong predictors  |            |                             |                                |                |
| None                    | 97 (36.2)  | 39 (40.2)                   | 58 (59.8)                      | < 0.001        |
| One                     | 104 (38.8) | 80 (76.9)                   | 24 (23.1)                      |                |
| Two                     | 58 (21.6)  | 51 (87.9)                   | 7 (12.1)                       |                |
| Three                   | 9 (3.4)    | 9 (100)                     | 0 (0)                          |                |
| Strong predictors       |            |                             |                                |                |
| None                    | 27 (16.4)  | 3 (11.1)                    | 24 (88.9)                      | < 0.001        |
| One                     | 78 (47.3)  | 50 (64.1)                   | 28 (35.9)                      |                |
| Two                     | 60 (36.4)  | 50 (83.3)                   | 10 (16.7)                      |                |

ERCP: Endoscopic retrograde cholangiopancreatography.

the presence of choledocholithiasis on ERCP and the risk group ( $P < 0.001$ ) (Table 3). The odds ratio (OR) for choledocholithiasis in high risk patients was 7.89 (95%CI: 4.36-14.32). The combination of any two or all very strong predictors elevated the probability of choledocholithiasis for 87.9% (51/58) and 100% (9/9), respectively. The combination of both strong predictors presented 83.3% (50/60) of probability of choledocholithiasis.

#### **Sensitivity, specificity, positive predictive values and negative predictive values for choledocholithiasis**

Cholangitis was the parameter that had the higher specificity (96.6%), however for the same parameter the sensitivity was low. Total bilirubin > 4 mg/dL or the presence of CBD stones on US also presented a good specificity (89.9% and 70.8%, respectively). The PPV was high for very strong predictors, mainly clinical ascending cholangitis (PPV 91.7%) and CBD stones on US (PPV 91.7%). The high risk group had a high sensitivity (86%) and PPV (79.8%), but low specificity (56.2%) for the presence of CBD stones (Table 4).

## **DISCUSSION**

According to ASGE guidelines, a patient stratified as

high risk has > 50% of probability of choledocholithiasis<sup>[12]</sup>. In our study, patients stratified as high risk following ASGE criteria had 79.8% probability of choledocholithiasis. These results are consistent with those presented in the study by Rubin *et al.*<sup>[13]</sup>. All the very strong predictors (clinical ascending cholangitis, CBD stones on US or total bilirubin > 4 mg/dL) presented a statistically significant association with the presence of choledocholithiasis. The combination of any of two or three very strong predictors increased the probability of choledocholithiasis for 87.9% and 100%, respectively.

Transabdominal ultrasound is the most commonly used initial imaging modality for suspected biliary stones. In our study, the presence of CBD stones detected during the US evaluation presented an OR of 11.25 for choledocholithiasis. The diagnosis of choledocholithiasis is often difficult, with the sensitivity for the detection of CBD stones by US ranging from 20% to 80%<sup>[14]</sup>. The diagnostic accuracy of US is operator dependent but it is also influenced by some clinical features of patients (shadowing from bowel gas, overweight and stone size)<sup>[14]</sup>.

In our study, the combination of strong predictors (dilated CBD on US, total bilirubin 1.8-4 mg/dL) presented 83.3% of probability of choledocholithiasis confirmed at ERCP. Strong predictors presented a sta-

**Table 4 Sensitivity, specificity, positive predictive values and negative predictive values for choledocholithiasis**

| Variable                       | Sensitivity | Specificity | PPV  | NPV  |
|--------------------------------|-------------|-------------|------|------|
| Very strong predictors         |             |             |      |      |
| Clinical ascending cholangitis | 18.4        | 96.6        | 91.7 | 37.0 |
| Common bile duct stone on US   | 55.9        | 89.9        | 91.7 | 50.3 |
| Total bilirubin > 4 mg/dL      | 42.5        | 70.8        | 74.5 | 37.8 |
| Strong predictors              |             |             |      |      |
| Total bilirubin 1.8-4 mg/dL    | 61.1        | 66.6        | 75   | 51.2 |
| Dilated common bile duct on US | 83.8        | 49.4        | 76.9 | 60.3 |
| Moderate predictors            |             |             |      |      |
| Abnormal liver function test   | 89.9        | 21.3        | 69.7 | 51.3 |
| Age > 55 yr                    | 79.3        | 38.2        | 72.1 | 47.9 |
| Gallstone pancreatitis         | 20.1        | 69.7        | 57.1 | 30.2 |
| High risk group                | 86          | 56.2        | 79.8 | 66.7 |
| Intermediate risk group        | 13.9        | 46          | 34.2 | 21   |

PPV: Positive predictive values; NPV: Negative predictive values; US: Ultrasonography.

tistically significant association with the presence of choledocholithiasis, which is in line with other previously published data<sup>[15-18]</sup>. The OR for choledocholithiasis in a patient with a CBD dilation was 5.06. However, the CBD dilation should always be interpreted according to patient characteristics, particularly previous cholecystectomy and age<sup>[19-21]</sup>. Previous studies<sup>[15-17,22,23]</sup> have reported some utility of serum bilirubin levels as a predictor of CBD stones. In this study, a bilirubin value between 1.8-4 g/dL had an OR of 3.15 and a specificity of 66.6% for choledocholithiasis. The specificity increased to 70% when the bilirubin value was > 4 mg/dL. These results are in agreement with those previously reported by ASGE guidelines<sup>[12]</sup>.

Individually, moderate predictors, such as abnormal liver function test and age > 55 years, presented a statistically significant association with the presence of choledocholithiasis in our series and a sensitivity of 89.9% and 79.3% for the prediction of choledocholithiasis on ERCP. In a study by Barkun *et al.*<sup>[16]</sup>, abnormal liver function tests, such as alkaline phosphatase > 300 units/L and AST > 120 units/L present a sensitivity of 79% and 81% to predict choledocholithiasis, respectively. At the same study, age > 55 years, only presented a sensitivity of 57%, however, when combined with other predictors (elevated bilirubin and CBD dilation on US) the model predicted with 94% of probability the presence of choledocholithiasis.

As previously reported by other authors<sup>[13,24]</sup>, also in our results the diagnosis of gallstone pancreatitis was not related with the presence of choledocholithiasis at ERCP ( $P > 0.05$ ). Stone size may be an explanation, as larger stones are less likely to migrate<sup>[24]</sup> and the small gallstones, that most commonly are the source of pancreatitis<sup>[25]</sup>, frequently pass spontaneously. Some studies have reported that in the absence of cholangitis, patients with gallstone pancreatitis do not benefit from early ERCP<sup>[26,27]</sup>.

In patients stratified into the intermediate and low risk group, the probability of choledocholithiasis is

10%-50% and < 10%, respectively<sup>[12]</sup>. In this study, the probability of choledocholithiasis was 34.2% (25/73) and 0 (0/2) for intermediate and low risk groups, respectively. For these risk groups the sensitivity, specificity, PPV and NPV did not show values with clinical interest. In the intermediate risk group, ASGE guidelines<sup>[12]</sup> recommended less invasive options for detecting choledocholithiasis, such as MRCP or EUS. The two techniques showed a good sensitivity and specificity for choledocholithiasis<sup>[28,29]</sup>, so deciding which test should be performed first depends on various factors such as availability, cost, patient-related factors and the suspicion for a small stone. Because it is noninvasive, MRCP is the first test performed to look for CBD stones. However, for small CBD stones (< 5 mm) the sensitivity of MRCP is lower<sup>[30]</sup>, so, if the MRCP is negative, but the suspicion for a common bile duct stone remains moderate to high, EUS is an appropriate next step.

In conclusion, our study confirms that the combination of choledocholithiasis predictors, according to ASGE guidelines<sup>[12]</sup>, enables risk stratification of patients based on the likelihood for the presence of choledocholithiasis. However, for high risk patients the specificity was still low (56.2%), with 39 patients (20%) false positive, meaning that a significant proportion of patients will be submitted to ERCP unnecessarily. In the future, the inclusion of new predictors or different combinations of previous predictors will be essential to improve the classification of patients as high risk, obviating the need of other imaging tests (MRCP/EUS) before ERCP. However, at this point, it seems advisable that also "high risk" patients undergo further testing with MRCP and/or EUS before being submitted to ERCP, similarly to those patients with "intermediate risk", while for patients with "low-risk" of choledocholithiasis a watchful waiting strategy seems adequate.

## COMMENTS

### Background

Patients suspected of having choledocholithiasis are diagnosed with a combination of laboratory tests and/or imaging studies. Endoscopic retrograde cholangiopancreatography (ERCP) has been established as the standard method for the management of bile duct stones, but it may be associated with substantial morbidity and mortality. In the evaluation of suspected choledocholithiasis, the American Society for Gastrointestinal Endoscopy (ASGE) proposes to stratify a patient as high risk, intermediate risk or low risk for having choledocholithiasis. Subsequent management will vary depending on the patient's level of risk.

### Research frontiers

In this study, the authors aimed to assess the practical applicability and to validate the current ASGE guidelines in a population of patients undergoing ERCP for suspected choledocholithiasis.

### Innovations and breakthroughs

The study confirms that the combination of choledocholithiasis predictors, according to ASGE guidelines may improve risk estimation of choledocholithiasis and should be considered to optimize patients' selection for ERCP. However, even in the "high risk group" the specificity was low (56.2%), meaning that a significant proportion of patients will still perform ERCP unnecessarily.

### Applications

The results of this study suggest that the inclusion of new predictors of choledocholithiasis or different combinations of previous predictors will be essential to improve the classification of patients as high risk, obviating the need of other imaging tests before endoscopic retrograde cholangiopancreatography. Thus, at this point, it seems advisable that also "high risk" patients undergo further testing before being submitted to ERCP, similarly to those patients with "intermediate risk", while for patients with "low-risk" of choledocholithiasis a watchful waiting strategy seems adequate.

### Terminology

Choledocholithiasis is defined as the occurrence of stones in the bile duct and has a propensity for life-threatening complications such as cholangitis and acute pancreatitis. Endoscopic retrograde cholangiopancreatography is a technique that combines the use of endoscopy and fluoroscopy to diagnose and treat problems of the biliary or pancreatic ductal systems. It has evolved from a diagnostic procedure to an almost exclusively therapeutic technique.

### Peer-review

Title and running title accurately reflects the topic and contents of the paper key words.

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