

# Intermediate Risk of Choledocolithiasis: Are We on the Right Path?

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## Research Article

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# Abstract

## Background

Choledocolithiasis is the presence of stones in the bile duct, commonly associated with cholelithiasis, with an incidence of 5-18%. Risk of choledocolithiasis should be assessed in every patient who must undergo cholecystectomy to define the next step, which can be either surgical or endoscopic. The American Gastroenterology Society (ASGE) proposed a predictor scale of choledocolithiasis based on ultrasound findings, liver function tests, and the presence of pancreatitis and/or cholangitis. Therefore we aim to describe our experience managing patients with intermediate risk of choledocolithiasis according to the ASGE guidelines and actual presence of bile duct stones in magnetic resonance cholangiopancreatography.

## Methods

A retrospective observational study with a prospective database was conducted. Patients over 18 years old who complied with inclusion criteria between January and December 2019, were registered. Descriptive statistics of all study parameters were provided. Analysis included socio demographic data, laboratory values and imaging. Bivariate, multivariate and ROC analysis was performed.

## Results

327 patients with biliary disease were classified as having intermediate risk for choledocolithiasis. Half the patients were at least 65 years old (iqr 20). All patients underwent MRI cholangiography. 24.77% were diagnosed with choledocolithiasis. Bile duct dilation was documented in only 3.06% of cases. Diagnosis of choledocolithiasis is associated with age OR: 1.87 (p 0.02), alkaline phosphatase OR: 2.44 (p 0.02) and bile duct dilation < 6 mm OR: 14.65 (p 0.00).

## Conclusions

There is a high proportion of patients classified as intermediate risk who did not have choledocolithiasis by colangioresonance. There is a persistently high variability in accuracy of imaging techniques in intermediate risk patients. Therefore, enhancing the criteria to define intermediate risk for patients in order to optimize resources is of paramount importance.

## Background

The gallbladder is a small pouch that sits under the liver and stores bile [1]. Bile aids in the fat digestion process, during which cholesterol can deposit and form thick crystals (sludge) or stones (gallstones), formation of stones in the gallbladder is called cholelithiasis [1, 2]. Additionally, gallstones can get plunged in the gallbladder, in the cystic duct, or in the common bile duct [1, 2]. Cholelithiasis is a common disease, occurring in 5–22% people in the western countries, among 8–20% combined with common bile duct stone (CBDS) [3, 4]. Choledocolithiasis is the presence of stones in the bile duct, commonly

associated with cholelithiasis, with an incidence of 5–18% [5, 6]. However, it also presents in patients with a history of cholecystectomy, with an incidence of 10 to 18% [7]. Choledocolithiasis is a frequent cause of hospitalization which may lead to cholangitis and gallstone pancreatitis [3].

In order to avoid pancreatitis and cholangitis, every patient with cholelithiasis planning to undergo cholecystectomy, should have its risk of preoperative choledocolithiasis figured, thus defining the next step, which can be either surgical or endoscopic [5]. Therefore, the American Gastroenterology Society (ASGE) proposed some predictors based on ultrasound findings, liver function tests, and the presence of pancreatitis and/or cholangitis [8, 9]. According to the ASGE criteria, patients with cholelithiasis have been classified as having high, intermediate or low risk of concomitant choledocolithiasis [9]. The most controversial group are the patients classified as intermediate risk due to a wide range of diagnostic and management pathways [8]. According to the flow chart proposed by ASGE, patients with low risk of choledocolithiasis should undergo cholecistectomy, while patients with high risk of choledocolithiasis should undergo endoscopic retrograde pancreatography as a diagnostic and therapeutic procedure [10, 11]. ASGE score is widely used worldwide, and the 2019 update is focused on reducing the amount of unnecessary ERCP but not the unnecessary use of the MRCP [12]. Intermediate risk involves a large proportion of patients, therefore impacting prompt management and increasing health costs [13].

The intermediate risk group for choledocolithiasis constitutes a therapeutic challenge, due to possible need of presurgical biliary imaging [12–13]. Magnetic resonance cholangiopancreatography (MRCP), has a 85%-92% sensitivity and 93%-97% specificity [14, 15] but it requires the provision of a resonator, the time to perform it, increased costs and the interpretation of an experienced radiologist [11, 12, 13]. It is worth clarifying that the gold standard for the diagnosis of choledocolithiasis is endoscopic retrograde cholangiopancreatography (ERCP), but with non-negligible risks (5–10% morbidity) thus, it should be limited to high risk patients [14]. On the other hand, despite its high sensibility the use of endoscopic ultrasound is not widely available and is limited to some institutions [15, 16, 17].

The purpose of this study is to describe our experience managing patients with intermediate risk of choledocolithiasis according to the ASGE guidelines and the confirmation of bile duct stones with magnetic resonance cholangiopancreatography (MRCP).

## Methods

Following Institutional Review Board approval, all patients over 18 years old who were diagnosed with medium risk of choledocolithiasis according to the 2010 ASGE guidelines between January and December 2019, were registered. The present study was performed in a single institution. A retrospective analysis of patients who complied with inclusion criteria was made for the study. Ethical compliance with the Helsinki Declaration, current legislation on research Res. 008430 – 1993 and Res. 2378 – 2008 (Colombia) and the International Committee of Medical Journal Editors (ICMJE) were ensured under our Ethics and Research Institutional Committee (IRB) approval. The study was approved by Universidad del Rosario – Hospital Universitario Mayor Méderi IRB

Data obtained included patients demographics, liver function tests, additional diseases, imaging studies obtained and its results. Descriptive statistics of all study parameters were provided. Data was analyzed using STATA 17 software. Continuous data were summarized by their mean, standard deviation, median and interquartile range. Categorical data were summarized by their frequency and proportion. Bivariate analysis was performed. Qualitative variables were analyzed using chi-square statistics (Fisher's exact test when appropriate). Quantitative variables were analyzed, based on normality, with Spearman's or Pearson's associations correlation coefficient accordingly. Bivariate analysis between qualitative and quantitative variables was performed using Mann-Whitney test and t-test for independent samples. Binary multivariate analysis was performed with significant variables found in the bivariate. ROC analysis was used to determine cutoff points for relevant liver tests, a new multivariate analysis was performed with new cutoff points.

## Results

From January to December 2019, a total of 342 patients with biliary disease were classified as having intermediate risk of choledocolithiasis. 15 patients were excluded as they were initially misclassified as intermediate risk, obtaining a total of 327 (**Figure 1**) patients with intermediate risk of choledocolithiasis according to the ASGE 2019 guidelines [12]. Median age was 65 (iqr 20) years old, 70,72 % were female and 29,28 % male. Half the patients had a time of symptomatology onset to consultation of 2 days. Within the paraclinical tests, leukocytosis was an important parameter, with 50% of patients presenting more than 10,760/mm<sup>3</sup> (iqr 5,705) leukocytes. Median total bilirubin was 1.415 mg / dL (iqr 1.505), usually at the expense of direct bilirubin with a median of 0.755 mg/dL (iqr 1.105). Liver profile was slightly altered in our population, with median AST, ALT and alkaline phosphatase of 121 (iqr 291), 127 (iqr 287.5) and 165 (iqr 156) IU/L, respectively (**Table 1**).

All patients underwent magnetic resonance cholangiography, while the vast majority (97.5%) had a previous hepatobiliary ultrasound (**Table 2**). Of the 100% of patients taken to MRI cholangiography, only 24.7% were diagnosed with choledocolithiasis (**Table 2**). 37.6% of the patients presented with cholecystitis, among which, 52.03% had a severity according to the Tokyo scale of II. 25.68% patients presented with pancreatitis at the time of diagnosis, the majority (47.6%) with a severity and organic failure according to the marshall scale of II (**Table 2**). A significant percentage of patients (48%) had previous intra-abdominal surgery, 10.7% were type 2 diabetic and 2.44% suffered from kidney disease.

Ultrasound findings indicated the presence of stones in the gallbladder or common bile duct, as well as the presence or absence of cholecystitis and bile duct dilation. According to these imaging findings, 49.38% of the patients had an ultrasound imaging diagnosis of cholelithiasis, 29.32% had concomitant cholecystitis and only 1.54% of the patients with bile duct dilation were reported in this initial study (**Table 3**). Among the patients taken to MRCP, a diagnosis of cholelithiasis was made in 32.42% of the patients. 25.08% had concomitant cholelithiasis and cholecystitis. Regarding the dilation of the bile duct, the percentage was 3.06% (**Table 4**).

Bivariate analysis was performed including the ASGE score variables for intermediate risk. Alkaline phosphatase OR: 1.00 (p 0.023), bile duct dilation > than 6 mm OR:12.48 (p = 0.000) , age OR: 1.02 (p = 0.01) and total bilirubin OR: 1.00 (p = 0.04) showed association with statistical significant value in the diagnosis of choledocolithiasis. Multivariate analysis with those variables was performed, results are summarized in **Table 5**.

ROC Curve including age, and alkaline phosphatase was performed seeking to define an appropriate cut-off value with acceptable sensitivity and specificity. The age value of 65 years old (S: 64.20% E: 51.63% AUC 0.59) and alkaline phosphatase 225 mg/dL , (S: 50.2% E: 70.46% AUC 0.62) and total bilirubin 1.6 mg/dL (S: 50% E: 55% AUC 0.62) were defined as cut-off points. In order to prove the statistical relationship of these cut off values in the diagnosis of choledocolithiasis, a multivariate regression was performed (**Table 6**). Age OR: 1.87 (p 0.02), alkaline phosphatase OR: 2.44 (p 0.02) and bile duct dilation < 6 mm OR: 14.65 (p 0.00) (**Table 6**).showed stronger association with the diagnosis; total bilirubin did not show statistically significant relationship with choledocolithiasis p 0.391.

## Discussion

Criteria for risk stratification proposed by the American Society of Gastrointestinal Endoscopy (ASGE) are frequently used worldwide. Following ASGE guidelines in 2010, patients are routinely categorized according to the probability of choledocolithiasis in low risk (<10%), intermediate risk (10%-50%) and high risk (>50%) [9]. Patients with intermediate risk benefit from additional biliary imaging [18,19] and options for this include magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS) and intraoperative cholangiography (IOC) [17]. In their updated guidelines of 2019, ASGE suggests either EUS or MRCP to confirm choledocolithiasis in intermediate risk patients [20]. The differences between both classifications change the risk in 6 of our patients as described in **Table 7**.

Moreover, the wide range of imaging studies paired with their varying sensitivity and specificity, has enriched the discussion regarding subsequent steps after intermediate risk classification. Meeralam et al. published a meta-analysis comparing EUS and MRCP diagnostic accuracy in which, albeit cost effectiveness and adverse events were not taken into consideration, MRCP provided good diagnostic accuracy with a sensitivity and specificity of 87% and 92% respectively [21]. By protocol and availability at our institution, patients with intermediate risk for choledocolithiasis are assessed by MRCP. From 327 MRCP performed in this study, up to 24,9% were positive for choledocolithiasis. Toro-Calle et al, found a choledocolithiasis frequency of 26.6% in patients with intermediate risk, which is comparable with our results [22]. It is worth noting that the seemingly low frequency of choledocolithiasis in this group of patients may be related to lower sensitivity (33% to 71%) of MRCP in the setting of small stones (<3mm) [23,24], which was present in up to 4.72% of our patients according to US findings. Yet, Badger et al found that most of the patients that underwent MRCP were followed with a more invasive test in 82% of cases, increasing the conflicting findings among literature [22].

Liver chemistries are measured as indirect markers of hepatobiliary disease [25], standard markers include AST, ALT, alkaline phosphatase and bilirubin as moderate predictors of choledocolithiasis in ASGE guidelines [9]. Aminotransferases including AST and ALT are enzymes involved in the transfer of amino groups of aspartate and alanine to ketoglutaric acid and referred to as transaminases [25]; regarding this predictors for intermediate risk, there is inconsistency in literature findings, some studies have shown that gamma glutamyl transferase (GGT) has the highest sensitivity, others demonstrate superiority in ALT for choledocolithiasis [26]. In our institution, median values of total bilirubin and alkaline phosphatase were within normal limits, whereas median values of transaminases were approximately 3 times over cutoff level; GGT levels were not measured. AST and ALT were elevated more than threefold in at least 50% of patients with choledocolithiasis; nonetheless no statistical significance correlation was found. Zare et al, in a prospective study performed in 350 patients for the assessment of liver function tests in the diagnosis of common bile duct stones in patients with cholecystitis found ALT as an independent predictor of cholelithiasis (OR: 2; P=0.04) [27]. More recently, novel predictive scores are being proposed showing AUC of 0.77 and 0.76 for AST and ALT respectively in a cohort of 1089 patients [28]. Other descriptive studies have shown AST as the least sensitive parameter altered approximately 50.8% of times [29]. Thus, despite the discrepancy of liver enzyme specificity, ongoing elevation of liver tests can provide support on deciding further imaging studies [26].

Common bile duct (CBD) stones should be diagnosed on time, despite the lack of a consensus on the usefulness of liver enzymes measurement as in CBD stones; multiple studies suggest a positive association between: Alkaline phosphatase, alanine transaminase (ALT) and choledocolithiasis [26]. Isherwood et al, described the association between choledocolithiasis and echographic finding of common bile duct dilation more than 6 mm OR 3.16 (p=0.06), and elevated values of alkaline phosphatase OR 4.64 (p<0.00), and alanine transaminase (OR 5.40 p<0.001)[26]. Nonetheless, despite in our study CBD dilation had an increased odds ratio (12,48 IC 3.97 - 39.18), transaminases did not show an statistically significant relationship as a diagnosis predictor.

Finally, our results and the comparison with the literature, shows the complexity in the diagnosis process, with important covariates that could mislead a timely diagnosis, and could delay the surgical management of cholelithiasis; these exposes the need of more specific and sensible predictive tools for CBD stones.

Among limitations of this study are its retrospective nature, the lack of stronger associations between the variables and the outcome and the scarcity of previous studies to compare our findings. Even though a considerable group of patients with cholelithiasis have concomitant intermediate choledocolithiasis the risk the scores available still give very loose recommendations regarding follow-up steps.

## Conclusion

There is a high percentage of patients classified as intermediate risk who do not have choledocolithiasis evidenced in colangiorenance. There is a persistently high variability in accuracy of imaging

techniques in intermediate risk patients. CBD Dilation, Alkaline phosphatase, and age, should be highmarked as predictive tools into the intermediate risk score, and could be a feasible tool to predict choledocolithiasis with acceptable sensitivity and specificity. Further studies are needed to confirm our results.

## Declarations

### AVAILABILITY OF MATERIALS AND DATA

The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

### AUTHORS CONTRIBUTIONS

FG, FG and SR had the research idea, designed the work, interpreted the analyzes, and wrote the paper. DC, LR, DJ, LN and CR found the databases, analyzed the information, and interpreted the preliminary analyzes. FG, LR, DC, DV, RN and MV analyzed the information, interpreted the results, and wrote the paper SR, DC and RMN made substantial contributions to the conception, designed the work, analyzed the information, interpreted the analyzes, wrote, and approved the final manuscript. All authors revised and gave the final Approval to the manuscript.

### COMPETING INTERESTS

Drs. Felipe Giron, Lina Rodríguez, Danny Conde, Carlos Rey, David Venegas, Marco Vanegas, Laura Niño, Fernando Gutierrez, Ricardo Manuel Nassar, Daniel Jimenez and Susana Rojas have no conflicts of interest or financial ties to disclose.

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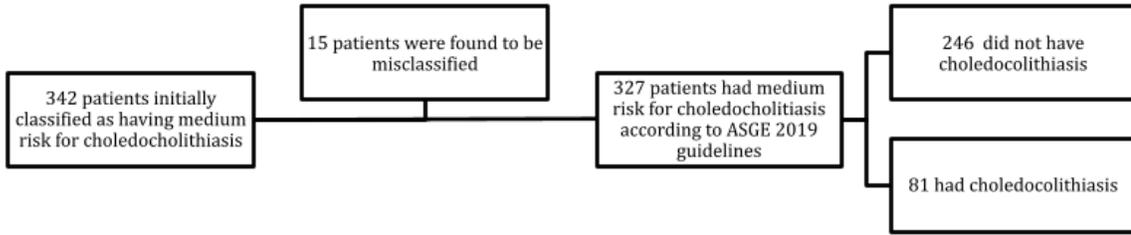
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## Tables

Due to technical limitations, table 1-7 is only available as a download in the Supplemental Files section.

## Figures



**Figure 1**

Patients inclusion process

## Supplementary Files

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