Electronic Physician (ISSN: 2008-5842) http://www.ephysician.ir
October-December 2019, Volume: 11, Issue: 4, Pages: 7610-7619, DOI: http://dx.doi.org/10.19082/7610

# Sensitivity and specificity of clinical, biochemical, and radiological predictors of common bile duct stones in patients who underwent endoscopic retrograde cholangiopancreatography: a binary logistic regression analysis

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**Type of article:** Original

## Abstract

**Background:** Gallbladder stones are one of the most common of today's health-related problems. Prediction of Common Bile Duct Stones (CBDS) permits better management of those patients.

**Objective:** The aim of this study was to determine the sensitivity and specificity of various predictors of CBDS.

**Methods:** This cross-sectional study was conducted on patients who underwent Endoscopic Retrograde Cholangiopancreatography (ERCP) for suspected CBDS at King Fahd Hospital of the University (Al-Khobar, Saudi Arabia from 2006 to 2018. Based on the presence or absence of specific predictive features as per the American Society for Gastrointestinal Endoscopy (ASGE) guidelines, we stratified the patients into high, intermediate, and low-risk of harboring CBDS. Data were analyzed by IBM© SPSS© version 21, using Chi-square test, Mann–Whitney U test, Wilcoxon signed rank test, and receiver operating characteristic curve analysis. Also, binary logistic regression was performed to determine the independent predictors, and p-value <0.05 was considered statistically significant. Sensitivity, specificity, likelihood ratios, accuracy, positive predictive value, and negative predictive value were calculated for potential predictors of CBD stones.

**Results:** One hundred forty-two patients were included in the study, 76 patients (53.5%) had choledocholithiasis [64.4% males, 45.8% females (p=0.028)] and 66 patients (46.5%) had normal CBD on endoscopic retrograde cholangiopancreatography. In the choledocholithiasis group, the proportion of jaundice was significantly higher 61% (p=0.037), abdominal pain was reported in 54.7% of the patients (p=0.126), itching in 75% (p=0.119), change in the color of stool and urine was reported in 57.1% (p=0.718), 61.4% (p=0.209) of the patients, respectively. Positive Murphy's sign was seen in 37.4% of the patients who had CBDS (p=0.234). Visualization of CBD stones on trans-abdominal ultrasonography was the best predictor for the presence of CBDS (adjusted OR: 4.744, sensitivity: 34%, specificity: 92%, p<0.0001), followed by CBD diameter (adjusted OR: 1.350, sensitivity: 82%, specificity: 49%, p=0.000). Among Liver function tests (LFTs), total bilirubin >1.8 mg/dl, direct bilirubin >2 mg/dl, GGTP >281 U/L, and ALP >149 U/L are considered reliable predictors for choledocholithiasis.

**Conclusion:** Visualization of CBD stones on trans-abdominal ultrasonography was the best predictor for the presence of CBDS followed by CBD diameter. CBD diameter ≥7 mm on ultrasonography in cases that the patient did not undergo cholecystectomy and more than 1 cm in cases that the patient underwent cholecystectomy are suggestive of CBDS. In presence of either conditions, we suggest proceeding to more invasive and therapeutic procedures such as ERCP.

**Keywords:** Gallstones, Common Bile Duct; Liver Function Tests; Ultrasonography; Jaundice

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Received: July 28, 2019, Accepted: October 23, 2019, Published: December 2019
iThenticate screening: October 23, 2019, English editing: November 06, 2019, Quality control: November 17, 2019
This article has been reviewed / commented by three experts
Ethics approval: KFHU (Ref: 2017-596-MED-NF)

**Abbreviations / Acronyms:**
**ACC:** Acute Calculous Cholecystitis; **ALP:** Alkaline Phosphatase; **ALT:** Alanine Transaminase; **ASGE:** American Society for Gastrointestinal Endoscopy; **AST:** Aspartate Aminotransferase; **AUC:** Area Under the Curve; **CBDS:** Common Bile Duct Stones; **CDL:** Choledocholithiasis; **D.Billi:** Direct Bilirubin; **ERCP:** Endoscopic Retrograde Cholangiopancreatography; **GGTP:** Gamma-Glutamyl Transferase; **LDH:** Lactate Dehydrogenase; **NPV:** Negative Predictive Value; **PPV:** Positive Predictive Value; **PT:** Prothrombin Time; **PTT:** Partial Thromboplastin Time; **MRCP:** Magnetic Resonance Cholangiopancreatography; **T.Billi:** Total Bilirubin; **WBC:** White Blood Cell Count.

## 1. Introduction

One of the most common of today's health-related problems is Gallbladder stones, which is associated with increased morbidity and sometimes even mortality. With prevalence of 10–20% in adults in developed countries, gallstone disease is one of the most prevalent and costly gastrointestinal tract disorders in the world (1). Prevalence and epidemiology of gallstone diseases could be helpful to clinicians, policy makers, and researchers. Studies regarding its prevalence in the Middle East are scarce (2-4). The overall prevalence of gallstone disease in Riyadh city was 8.6%. Old age, female gender, sedentary lifestyle and obesity are key factors in the progression of gallstones (2). Common bile duct stones (CBDS) are either primarily originating within the duct, or secondarily, due to the passage of the gallstones through the cystic duct. At the time of diagnosis of symptomatic Gallbladder stones, about 10-20% of the patients are found to have concurrent CBDS (5). Secondary CBDS are the most common, it can be asymptomatic with an incidental discovery during the evaluation of gallstones or can lead to various symptoms and complications including acute cholangitis, biliary pancreatitis, bacterial sepsis, and if the obstruction is prolonged it may cause secondary biliary cirrhosis and portal hypertension (5). Thus, it is essential to diagnose CBDS for early management and prevention of such complications. Various indicators of the presence of CBDS are recognized including clinical presentation, biochemical laboratories, and radiological imaging, each with different sensitivity and specificity as suggested by previous studies (6). It is reported that cholangitis has a sensitivity of 42% and a specificity of 100%, and jaundice has a sensitivity of 69% and a specificity of 89% (6). However, to the best of our knowledge, there is no single best indicator of CBDS. Both Endoscopic Retrograde Cholangiopancreatography (ERCP) and Magnetic Resonance Cholangiopancreatography (MRCP) are good modalities for the diagnosis of CBDS, but still, they cannot be depended on routinely because of the invasiveness in cases of ERCP and high cost in cases of MRCP (7). Therefore, owing to this lack of data, the current study was carried out to evaluate each indicator of CBDS independently and determine those with the highest sensitivity and specificity, which can be depended on for the diagnosis and decision making as to whether or not to proceed for more invasive investigations. Our secondary objective was to establish a clear cut-off point regarding the biochemical parameters, which can be used to predict the presence of CBDS.

## 2. Material and Methods

### *2.1. Research design and patients*

This cross-sectional study was conducted on all patients (n=257) who underwent ERCP for suspected CBD stones between January 2006 and January 2018. After applying the exclusion criteria, the study ended up with 142 patients. Then, patients were allocated into two groups as follows: 1) patients with CBD stones, and 2) patients without CBD stones, based on the presence or absence of CBD stones on the ERCP report. Using the ASGE guidelines, patients were stratified into high-risk (greater than 50% incidence of choledocholithiasis), intermediate-risk (10%-50% incidence), and low-risk (less than 10% incidence) categories based on the presence of specific predictive features. Very strong predictors of choledocholithiasis are evidence of a CBD stone on transabdominal ultrasound, clinical ascending cholangitis, and a bilirubin level higher than 4 mg/dL, while strong predictors are a dilated CBD on ultrasound (greater than 6 mm with gallbladder in situ) and a bilirubin level from 1.8 to 4 mg/dL.

### *2.2. Inclusion criteria*

This study included all patients who underwent ERCP for suspected CBD stones between January 2006 and January 2018 (Total Number=257).

### *2.3. Exclusion criteria*

The following were set as the exclusion criteria: 1) patients less than 18 years of age, 2) those who have a known cause of hepatocellular injury (whether bacterial, viral, autoimmune or drug-induced), 3) Mirrizi's syndrome, 4) a history of pancreatic surgery or hepatobiliary surgery with the exception of cholecystectomy, hepatobiliary system tumor, metastatic tumor, sclerosing cholangitis, alcoholic liver disease, pancreatitis other than biliary pancreatitis, 5) those who showed dilated common bile duct on ERCP with no intraductal stones, and 6) incomplete medical records or incorrect ICD codes

### *2.4. Sampling*

Using MedCalc Statistical Software version 16.4.3 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016), the minimum required sample size was calculated to be 57 for the choledocholithiasis group and 57 for the normal CBD group (at alpha 0.05, power 80%, assuming Area Under the Curve (AUC) = 0.65 and null hypothesis value 0.5).

### *2.5. Data Extraction*

A review of the involved patients' electronic medical records was done; missing data were completed from hard-copy. Clinical data at the time of admission and discharge were abstracted, including 1) demographics (age, sex, and nationality), history, physical findings (Murphy's sign), 2) biochemical data, and 3) radiographic findings. The obtained history data included jaundice, pruritus, abdominal pain, stool or urine color change and fever. The value of the following biochemical parameters were obtained: alkaline phosphatase (ALP), gamma-glutamyl transferase (GGTP), total bilirubin (T.Billi), direct bilirubin (D.Billi), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), white blood cell count (WBC), prothrombin time (PT) and activated partial thromboplastin time (PTT). Clinical and laboratory variables that were not recorded in the patients' charts were considered negative during data analysis. Results of abdominal ultrasound were reviewed regarding the CBD diameter (considered dilated if >7 mm for patients without a history of cholecystectomy and >1 cm for patients with a history of cholecystectomy), the presence or absence of CBD stones or gallbladder stones and the presence of acute cholecystitis. Stone size and number were not considered.

### *2.6. Statistical Analysis*

Statistical analysis was performed using the IBM© SPSS© Statistics version 21 (IBM© Corp., Armonk, NY, USA). Statistical significance was considered for a p-value <0.05 for two-tailed hypotheses. Data are presented as number and percentage for categorical data, and were compared by chi-square test. Quantitative data were presented as median and range and compared between the two groups using the Mann-Whitney U test. Before and after values were compared using Wilcoxon signed rank test. Receiver operating characteristic curve analysis (area under the curve [AUC]) was performed. Sensitivity, specificity, likelihood ratios, accuracy, positive predictive value, and negative predictive value were calculated for potential predictors of CBD stones. Binary logistic regression was performed to determine the independent predictors.

### *2.7. Ethics of research*

This study was reviewed and approved by the institutional review board (IRB) of KFHU (2017-596-MED-NF). The study did not need any specific consultation, administration of any investigational product, or change in the clinical management of the patients. All data was treated with respect to patients' anonymity and confidentiality.

## 3. Results

The study population included all patients who underwent ERCP for suspected CBD stones between January 2006 and January 2018 (n=257). After applying the exclusion criteria, the study ended up with 142 patients (41.5% were males, 58.45% were females), which covered the minimum requirement of the sample size. About half of them (76 patients, 53.5%) had Choledocholithiasis and 66 (46.5%) had normal common bile duct on ERCP (Non-Choledocholithiasis). Table 1 shows the demographical and clinical indicators of the patients by the group of diagnosis. The demographical distribution of the patients was approximately similar; the mean age was 47.01 (SD=19.7) in the choledocholithiasis group versus 41.45 (SD=13.7) in the non-choledocholithiasis group (p=0.05). CBDS were of a higher percentage among males 64.4% than among females 45.8% (p=0.028), the proportion of jaundice was significantly higher in the Choledocholithiasis group, seen in 61% of the patients (p=0.037), abdominal pain was reported in 54.7% of the choledocholithiasis group (p=0.126), itching was reported in 75% of the choledocholithiasis group (p=0.119). Change in the color of stool/urine was reported in 57.1%, 61.4% of the choledocholithiasis patients (p=0.718, 0.209 respectively). The fulfillment of the cholangitis triad (right upper quadrant pain, jaundice, and fever) was seen to be similar between the two groups (p=0.733). The stones were visualized in the CBD in 83.9% of the choledocholithiasis group (p=0.0001). Table 2 shows the biochemical laboratories of the patients at both admission and discharge. These parameters are measured twice, once at admission and again at discharge. A significant difference was found at the time of admission in some of the parameters. Patients with Choledocholithiasis had significantly higher blood levels of GGTP (p=0.007), total bilirubin (p=0.033), Prothrombin time (p=0.006) as compared to the Non- Choledocholithiasis.

**Table 1.** Demographic and clinical indicators of ERCP patients by presence of CBD stone

| Characteristics | | Diagnosis, n (%) | | p-value |
|---|---|---|---|---|
| | | Choledocholithiasis | Non- Choledocholithiasis | |
| Age; Mean (SD) | | 47.01 (19.7) | 41.45 (13.7) | 0.05 |
| Gender | Males | 38 (64.4) | 21 (35.6) | 0.028 |
| | Females | 38 (45.8) | 45 (54.2) | |
| Nationality | Saudi | 55 (52.4 ) | 50 (47.6) | 0.646 |
| | Non-Saudi | 21 (56.8) | 16 (43.2) | |
| Jaundice | Yes | 50 (61.0 ) | 32 (39.0 ) | 0.037 |
| | No | 26 (43.3) | 34 (56.7) | |
| Abdominal pain | Yes | 75 (54.7) | 62 (45.3) | 0.126 |
| | No | 1 (20.0) | 4 (80.0) | |
| Radiation of the abdominal pain to the right shoulder | Yes | 10 (62.5) | 6 (37.5 ) | 0.428 |
| | No | 65 (52.0) | 60 (48.0) | |
| Itching | Yes | 9 (75.0 ) | 3 (25.0 ) | 0.119 |
| | No | 67 (51.5) | 63 (48.5) | |
| Change in Stool color | Yes | 12 (57.1) | 9 (42.9) | 0.718 |
| | No | 64 (52.9 ) | 57 (47.1) | |
| Change in Urine color | Yes | 27 (61.4 ) | 17 (38.6 ) | 0.209 |
| | No | 49 (50.0) | 49 (50.0) | |
| Cholangitis | Yes | 10 (50.0) | 10 (50.0) | 0.733 |
| | No | 66 (54.1 ) | 56 (45.9) | |
| Positive Murphy's sign | Yes | 4 (36.4 ) | 7 (63.6) | 0.235 |
| | No | 72 (55.0 ) | 59 (45.0) | |
| Visualization of CBDS on ultrasonography | +ve | 26 (83.9) | 5 (16.1) | 0.0001 |
| | -ve | 50 (45.5) | 60 (54.5) | |

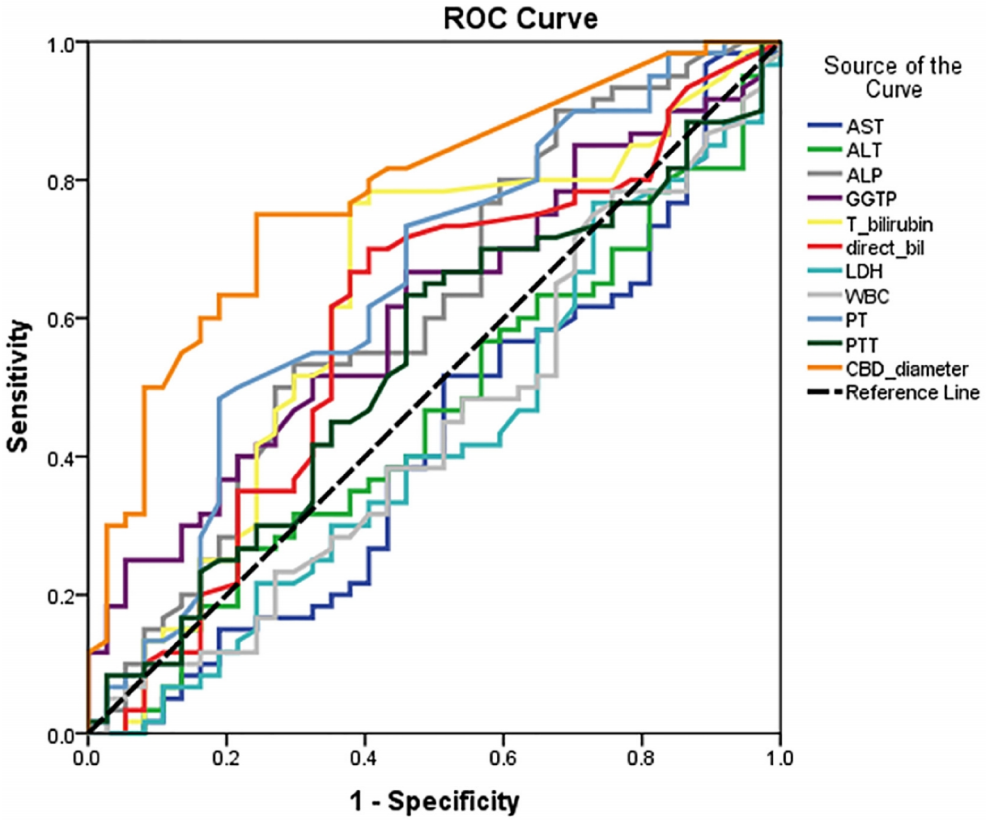


**Figure 1.** Receiver operating characteristic curves for individual clinical pathological parameters as predictors of common bile duct stones

**Table 2.** Biochemical parameters for the detection of CBDS in patients underwent endoscopic retrograde cholangiopancreatography

| Parameters | Choledocholithiasis; Median (min, max) | Non- Choledocholithiasis; Median (min, max) | p-value |
|---|---|---|---|
| AST at admission | 137 (14.0, 949.0) | 169 (16.0, 1730.0) | 0.199 |
| AST at discharge | 32.0 (6.3, 402.0)* | 38 (16.0, 583.0)* | 0.036 |
| Average change in AST | -103.0 (-933.0, 89.0) | -110.5 (-1695.0, 502.0) | 0.710 |
| ALT at admission | 189.0 (21.0, 940.0) | 216.0 (27.0, 1130.0) | 0.315 |
| ALT at discharge | 52.0 (12.0, 525.0)* | 92.0 (20.0, 838.0)* | 0.005 |
| Average change in ALT | -96.0 (-898.0, 122.0) | -100.0 (-865.0, 193.0) | 0.435 |
| ALP at admission | 243.0 (48.0, 910.0) | 207.0 (21.0, 976.0) | 0.099 |
| ALP at discharge | 144.0 (66.0, 612.0)* | 177.0 (60.0, 1090.0) | 0.053 |
| Average change in ALP | -85.0 (-675, 242) | -32.0 (-570.0, 331.0) | 0.002 |
| GGTP at admission | 437.0 (21.0, 2806.0) | 263.0 (19.0, 1061.0) | 0.010 |
| GGTP at discharge | 147.0 (22, 1313.0)* | 200.0 (35.0, 762.0)* | 0.053 |
| Average change in GGTP | -198 ( -1685 , 373) | -57 (-754 , 485 ) | 0.000 |
| TB at admission | 3.6 (0.2, 21.9) | 1.8 (0.2, 149.0) | 0.033 |
| TB at discharge | 0.9 (0.3, 11.0)* | 0.9 (0.2, 110.0)* | 0.877 |
| Average change in bilirubin | -2.4 (-14.9, 5.6 ) | -0.9 (-39, 13 ) | 0.037 |
| D.Bili at admission | 2.5 (0.1, 17.5) | 1.2 (0.1, 69.3) | 0.259 |
| D.Bili at discharge | 0.4 (0.1, 7.9)* | 0.4 (0.1, 43.0)* | 0.564 |
| Average change in D.Bili | -1.8 (-13.7, 2.3) | -0.7 (-26.3, 11.5) | 0.064 |
| LDH at admission | 219.0 (94.0, 969.0) | 259.5 (100.0, 1144.0) | 0.057 |
| LDH at discharge | 142.0 (94.0, 818.0)* | 151.0 (96.0, 384.0)* | 0.353 |
| Average change in LDH | -74 (-781.0, 263.0) | -103.0 (-1020.0, 173) | 0.221 |
| WBC at admission | 8.3 (3.0, 29.7) | 9.7 (3.0, 32.1) | 0.390 |
| WBC at discharge | 8.0 (2.0, 130.0)* | 7.0 (2.0, 26.0)* | 0.932 |
| Average change in WBC | -1.1 (-11.2,105.1) | -2.7 (-22.5, 5.9) | 0.041 |
| PT at admission | 13.0 (10.6, 55.7) | 12.0 (10.0, 24.6) | 0.006 |
| PT at discharge | 12.4 (10.2, 26.0) | 12.5 (10.7, 29.0)* | 0.961 |
| Average change in PT | -0.4 (-41.9,12.7) | 0.8 (-5.0, 4.4) | 0.015 |
| aPTTat Admission | 28.4 (22.2, 68.6) | 28.5 (21.6, 80.1) | 0.874 |
| aPTTat discharge | 28.0 (20.0, 39.0)* | 28.0 (12.0, 41.0) | 0.627 |
| Average change in aPTT | -0.4 (-40.1,13.2) | 1.0 (-13.2, 12.6) | 0.080 |
| CBD diameter | 10.0 (5.4, 98.0) | 6.4 (2.4, 89.0) | 0.000 |

*: statistically significant change at discharge comparing with the date admission. AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALP: Alkaline Phosphatase, D.Bili: Direct Bilitubin, GGTP: Gamma Glutamyl Transpeptidase, TB: Total Bilirubin, D-bilirubin: Direct Bilirubin, LDH: Lactate Dehydrogenase, WBC: White Blood Cell, PT: Prothrombin time, aPTT: Activated partial thromboplastin time. CBD: common bile duct

**Table 3.** Area under the curve (AUC) for the parameters of CBD stones from the ROC curve

| Parameter | AUC | 95% Cl | p-value |
|---|---|---|---|
| CBD diameter | 0.781 | 0.689 to 0.874 | 0.000 |
| Prothrombin time | 0.650 | 0.534 to 0.766 | 0.013 |
| Total Bilirubin | 0.625 | 0.505 to 0.745 | 0.040 |
| Alkaline Phosphatase | 0.616 | 0.498 to 0.734 | 0.055 |
| Gamma Glutamyl Transpeptidase | 0.610 | 0.498 to 0.723 | 0.055 |
| Direct Bilirubin | 0.590 | 0.469 to 0.711 | 0.139 |
| Activated partial thromboplastin time | 0.537 | 0.419 to 0.655 | 0.543 |
| Alanine Aminotransferase | 0.459 | 0.341 to 0.576 | 0.494 |
| Lactate Dehydrogenase | 0.426 | 0.307 to 0.545 | 0.223 |
| Aspartate Aminotransferase | 0.425 | 0.304 to 0.545 | 0.214 |

For parameters measured at the time of discharge AST (p=0.036) and ALT (p=0.005) showed significantly lower values for the Choledocholithiasis group as compared to the Non- Choledocholithiasis group. CBD diameter showed

a significantly higher value in the Choledocholithiasis group as compared to the Non- Choledocholithiasis group (p=0.000). For all the biochemical parameters studied, there was a significant decrease in the values at the time of discharge as compared to the value at the time of admission in the choledocholithiasis group upon removal of the obstructing CBD stones with p<0.05 except for the prothrombin time, and though there was a decrease at the time of discharge, that difference was not statistically significant (p=0.344) (Table 3). Table 3 shows the calculated area under the curve (AUC) for the various predictors of CBD stones. Figure 1 shows Receiver operating characteristic curves for individual clinical pathological parameters as predictors of common bile duct stones. The major findings of the study were that visualization of CBD stones on trans-abdominal ultrasonography was the best predictor for the presence of CBDS [adjusted OR 4.744, sensitivity 34%, specificity 92%, p<0.0001], followed by CBD diameter [adjusted OR 1.350, sensitivity 82%, specificity 49%, p=0.000]. CBD diameter ≥7 mm on ultrasonography in cases that the patient did not undergo cholecystectomy and more than 1 cm in cases that the patient underwent cholecystectomy are suggestive of CBDS independently, reaching a sensitivity of 82% and a specificity of 49%, AUC= 0.781, (p=0.000). This is important, as abdominal ultrasonography is a non-invasive and a cost-effective method compared to other radiological modalities. Of the liver function tests, total bilirubin had a sensitivity of 84% and a specificity of 25%, AUC=0.625, (p=0.040), GGTP with a sensitivity of 91% and a specificity of 13%, AUC= 0.610, (p=0.055) were the most reliable in predicting CBDS.

For assessment of risk stratification as in the American Society for Gastrointestinal Endoscopy (ASGE) criteria for evaluating patients with choledocholithiasis, evidence of a CBD stone on transabdominal ultrasound, clinical ascending cholangitis, and a bilirubin level higher than 4 mg/dL, are very strong predictors of choledocholithiasis. Bilirubin level from 1.8 to 4 mg/dL and dilated CBD on ultrasound (greater than 6 mm with gallbladder in situ) are strong predictors. Abnormal liver biochemical test other than bilirubin, age >55, and clinical gallstone pancreatitis are moderate predictors. In the current study, according to ASGE guidelines, the investigators determined the positive predictive value (PPV) to be as follows; of the 75 patients classified as very strong risk, 50 (66.7%) were found to have a CBD stone. Of the 60 considered as strong risk, 42 (70%) were found on ERCP to have a stone. The investigators determined the sensitivity and Kappa coefficient of the ASGE criteria to be 65.8% and 0.279 respectively for very strong-risk patients and 55.3%, 0.276 for strong-risk patients. Both had a fair agreement with ASGE criteria. After that, the diagnostic criteria of the variables studied in the current study and risk estimates of independent factors are shown in details in Tables 4 and 5. Entering age, gender, the studied clinical indicators, and the studied biochemical markers into a logistic regression, the only statistically significant independent factors were, positive results of stones by ultrasonography OR, 95% CI: 4.744 [1.162-19.373], and CBD diameter OR, 95% CI: 1.35 [1.129-1.615] (Table 4).

**Table 4.** Multivariate logistic regression analysis of parameters associated with differentiating choledocholithiasis from Non- choledocholithiasis

| Parameters | Coefficient (B) | SE | p-value | Adjusted OR | 95% CI |
|---|---|---|---|---|---|
| Positive results by US | 1.557 | 0.718 | 0.030 | 4.744 | 1.162-19.373 |
| CBD diameter | 0.300 | 0.091 | 0.001 | 1.350 | 1.129-1.615 |
| GGTP | 0.001 | 0.001 | 0.055 | 1.001 | 1.000-1.003 |

**Table 5:** Diagnostic accuracy of parameters for discriminating the presence and absence of CBD stones

| Parameter | Sensitivity, 95% CI | Specificity, 95% CI | PPV, 95% CI | NPV, 95% CI | LR+, 95% CI | LR-, 95% CI |
|---|---|---|---|---|---|---|
| AST (more than 41 U/L) | 0.83, 0.73-0.90 | 0.13, 0.07-0.24 | 0.54, 0.45-0.63 | 0.38, 0.21-0.59 | 0.95, 0.83-1.10 | 1.32, 0.59-2.98 |
| ALT (more than 65 U/L) | 0.77, 0.67-0.85 | 0.18, 0.10-0.29 | 0.53, 0.44-0.62 | 0.39, 0.24-0.58 | 0.94, 0.79-1.11 | 1.28, 0.65-2.52 |
| ALP (more than 141 U/L) | 0.85, 0.76-0.92 | 0.32, 0.22-0.44 | 0.60, 0.50-0.69 | 0.65, 0.47-0.79 | 1.25, 1.03-1.52 | 0.46, 0.24-0.89 |
| GGTP (more than 55 U/L) | 0.91, 0.82-0.95 | 0.13, 0.06-0.24 | 0.58, 0.49-0.67 | 0.5, 0.27-0.73 | 1.04, 0.92-1.17 | 0.74, 0.28-2.01 |
| Total Bilirubin (more than 1 mg/dl) | 0.84, 0.74-0.91 | 0.25, 0.25-0.37 | 0.56, 0.47-0.65 | 0.57, 0.39-0.73 | 1.12, 0.94-1.33 | 0.65, 0.33-1.27 |
| Direct Bilirubin (more than 0.4 mg/dl) | 0.79, 0.68-0.86 | 0.25, 0.16-0.37 | 0.57, 0.47-0.66 | 0.48, 0.32-0.65 | 1.05, 0.87-1.27 | 0.85, 0.46-1.58 |
| LDH (more than 190 U/L) | 0.64, 0.53-0.74 | 0.28, 0.18-0.41 | 0.55, 0.45-0.65 | 0.36, 0.23-0.51 | 0.89, 0.70-1.12 | 1.30, 0.77-2.19 |
| PT (more than 13.6 seconds) | 0.30, 0.20-0.42 | 0.65, 0.51-0.77 | 0.54, 0.38-0.70 | 0.4, 0.30-0.51 | 0.85, 0.49-1.47 | 1.08, 0.83-1.40 |
| CBD diameter * | 0.82, 0.72-0.89 | 0.49, 0.37-0.62 | 0.68, 0.58-0.77 | 0.68, 0.53-0.80 | 1.62, 1.23-2.14 | 0.36, 0.20-0.63 |

* (>7 mm for patients without a history of cholecystectomy and >1 cm for patients with a history of cholecystectomy). AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase. ALP: Alkaline Phosphatase. GGTP: Gamma Glutamyl Transpeptidase, LDH: Lactate Dehydrogenase, NPV: Negative Predictive Value; PPV: Positive Predictive Value; PT: Prothrombin time, CBD: common bile duct

In Table 6, we calculated the sensitivity, specificity, positive and negative likelihood ratios of different cut-off points of the biochemical parameter. Table 6 shows the sensitivity, specificity, positive and negative likelihood ratios of various biochemical markers of common bile duct stones, as well as the dilatation of the CBD on ultrasonography at different cut-off points. Accordingly, the following cut-off points are suggested. ALP higher or equal to 149 U/L had a sensitivity of 85.33% and a specificity of 31.75%, LR+1.2502, LR- 0.4620, GGTP of > 281 U/L (approximately three times the upper normal limits) showed a sensitivity of 65.33% and a specificity of 51.79%, LR+ 1.3551, LR- 0.6694, total bilirubin of ≥1.8 mg/dl, had 74.32%, sensitivity and 48.44% specificity, LR+1.4414, LR- 0.5301, direct bilirubin ≥2, with sensitivity of 61.33%, and a specificity of 58.33%, LR+1.4720, LR-0.6629, CBD diameter of 7 mm on ultrasonography had a sensitivity of 78.38% and specificity of 54.39%, LR+1.7183, LR-0.3976. The aforementioned cut-off points showed high sensitivity for the prediction of CBD stones, and therefore are suggested.

**Table 6.** The sensitivities and specificities of various cut-off points of alkaline phosphatase, gamma-glutamyltranspeptidase, total bilirubin, common bile duct diameters, direct bilirubin and prothrombin time in the diagnosis of CBDS

| Variables | Cutpoint | Sensitivity (%) | Specificity (%) | Classified (%) | LR+ | LR- |
|---|---|---|---|---|---|---|
| ALP | ≥149 | 85.33 | 31.75 | 60.87 | 1.2502 | 0.4620 |
| | ≥155 | 81.33 | 31.75 | 58.70 | 1.1916 | 0.5880 |
| | ≥164 | 80.00 | 36.51 | 60.14 | 1.2600 | 0.5478 |
| | ≥170 | 77.33 | 38.10 | 59.42 | 1.2492 | 0.5950 |
| | ≥174 | 74.67 | 39.68 | 58.70 | 1.2379 | 0.6384 |
| | ≥182 | 73.33 | 42.86 | 59.42 | 1.2833 | 0.6222 |
| GGTP | ≥233 | 69.33 | 48.21 | 60.31 | 1.3389 | 0.6360 |
| | ≥253 | 66.67 | 48.21 | 58.78 | 1.2874 | 0.6914 |
| | ≥281 | 65.33 | 51.79 | 59.54 | 1.3551 | 0.6694 |
| | ≥305 | 64.00 | 57.14 | 61.07 | 1.4933 | 0.6300 |
| | ≥309 | 60.00 | 57.14 | 58.78 | 1.4000 | 0.7000 |
| | ≥318 | 60.00 | 60.71 | 60.31 | 1.5273 | 0.6588 |
| Total Bilirubin | ≥1.8 | 74.32 | 48.44 | 62.32 | 1.4414 | 0.5301 |
| | ≥2.4 | 72.97 | 54.69 | 64.49 | 1.6104 | 0.4942 |
| | ≥2.6 | 71.62 | 59.38 | 65.94 | 1.7630 | 0.4780 |
| | ≥2.8 | 67.57 | 59.38 | 63.77 | 1.6632 | 0.5462 |
| | ≥2.9 | 64.86 | 60.94 | 63.04 | 1.6605 | 0.5766 |
| | ≥3.1 | 62.16 | 64.06 | 63.04 | 1.7297 | 0.5906 |
| Direct bilirubin | ≥1.2 | 68.00 | 46.67 | 58.52 | 1.2750 | 0.6857 |
| | ≥1.4 | 65.33 | 53.33 | 60.00 | 1.4000 | 0.6500 |
| | ≥1.8 | 62.67 | 55.00 | 59.26 | 1.3926 | 0.6788 |
| | ≥2 | 61.33 | 58.33 | 60.00 | 1.4720 | 0.6629 |
| | ≥2.1 | 57.33 | 60.00 | 58.52 | 1.4333 | 0.7111 |
| | ≥2.4 | 54.67 | 63.33 | 58.52 | 1.4909 | 0.7158 |
| PT | ≥11.6 | 89.06 | 30.43 | 64.55 | 1.2803 | 0.3594 |
| | ≥11.8 | 84.38 | 39.13 | 65.45 | 1.3862 | 0.3993 |
| | ≥12 | 76.56 | 47.83 | 64.55 | 1.4674 | 0.4901 |
| | ≥12.4 | 64.06 | 56.52 | 60.91 | 1.4734 | 0.6358 |
| | ≥12.7 | 56.25 | 60.87 | 58.18 | 1.4375 | 0.7188 |
| | ≥13 | 50.00 | 76.09 | 60.91 | 2.0909 | 0.6571 |
| CBD diameter | ≥7 | 78.38 | 54.39 | 67.94 | 1.7183 | 0.3976 |
| | ≥7.2 | 74.32 | 57.89 | 67.18 | 1.7652 | 0.4435 |
| | ≥7.7 | 72.97 | 59.65 | 67.18 | 1.8085 | 0.4531 |
| | ≥7.9 | 72.97 | 64.91 | 69.47 | 2.0797 | 0.4164 |
| | ≥8 | 72.97 | 66.67 | 70.23 | 2.1892 | 0.4054 |

ALP: Alkaline Phosphatase. GGTP: Gamma Glutamyl Transpeptidase, PT: Prothrombin time. CBD: common bile duct

**4. Discussion**

CBDS may be asymptomatic or may exhibit clinical signs such as obstructive jaundice and/or ascending cholangitis, which is a life-threatening consequence (8). Preoperative detection of CBDS permits better planning and results in better outcomes. A variety of tests have been proposed for the detection of CBDS pre-operatively, but up until now,

there is no single test or criteria that can diagnose CBDS definitively. Among all diagnostic modalities, ERCP had the highest sensitivity (96%), specificity (99.1%) in detecting CBDS (9). ERCP and MRCP are considered excellent modalities to diagnose CBDS, but they are not preferred for routine assessment due to the invasiveness, risk of complications and the cost burden, which have led researchers to search for an alternative.

Changes seen in the liver function values could raise the suspicion of possible CBDS, and it could be a useful parameter in diagnosing such condition. According to our findings, all the biochemical parameters except prothrombin time decreased significantly at the time of discharge as compared to the values at the time of admission in the choledocholithiasis group upon removal of the obstructing CBD stones, and this was consistent with a recent study that confirmed the benefit of LFTs to predict CBDS in patients with acute cholecystitis (AC). Elevated LFTs in patients with AC remain elevated in cases of CBDS until removal of the stones, and improve significantly in cases of not having CBDS before cholecystectomy, suggesting that follow up of LFTs is a useful predictor for CBDS (10). Our results concluded that among LFTs; total bilirubin >1.8 mg/dl, direct bilirubin >2 mg/dl, GGTP >281 U/L, and ALP >149 U/L, are considered reliable predictors for choledocholithiasis. Multivariate analysis showed that GGTP, ALP, and TB are independent predictors of CBDS, which support the previous finding (9, 11). In a prospective study by Reiss et al, it was reported that more than 60% of patients with higher than 3 mg/dl serum bilirubin had CBD stone (12). Shashanka M. Bose stated that as the bilirubin level increases, so does the incidence of CBDS (6). Interestingly, a serum bilirubin > 30 (2x Normal) was found not to be significant (p=0.145), in contrast to our findings (13). Per Videhult, in his prospective, population-based study of 1,171 patients who underwent cholecystectomy with IOC; revealed that raised serum ALP and bilirubin levels are the most reliable indicators and significantly predict CBDS with specificity 91%, sensitivity 52%, NPV 94%, PPV 42% (14). Similarly, according to our findings, the most reliable parameters in predicting CBDS were total bilirubin (sensitivity =84%, specificity =25%, AUC= 0.625, p=0.040), in addition to GGTP (sensitivity= 91%, specificity= 13%, AUC= 0.610, p=0.055). In contrast to other studies, bilirubin was the least specific and predictive of CBDS (15). However, false positive and false negative values are common especially in patients with a history of cholecystitis or pancreatitis, which indicates that LFTs elevation can be explained by other mechanisms not related to CBDS. Multiple studies have emphasized the usefulness of GGTP as a predictor for CBDS (16, 17). Ahn et al. pointed out that GGTP was the most reliable indicator (p<0.001), with an 80.6% sensitivity and 75.3% specificity at the cut-off level of 224 IU/L (10). Furthermore, GGTP> 90 units/l should raise the suspicion of CBDS (15).

Several studies have been conducted regarding the utility of clinical parameters in predicting CBDS. In our study, nearly half of the patients who had CBDS presented with abdominal pain and 61% had jaundice. A study evaluated different parameters to elucidate whether patients have acute calculous cholecystitis (ACC) or choledocholithiasis (CDL), the age was slightly higher in the ACC with CDL group than the ACC only group and the most predominant clinical presentation was right upper quadrant pain, yet could not differentiate patients with ACC from those with ACC⁄CDL (18). On the other hand, Per Videhult stated that age, gender, history of acute biliary pancreatitis or cholecystitis were not significant predictors for the presence of CBDS (14). Jaundice is an important sign of CBDS, but it requires some time to develop, is often transient, and fluctuates. Shashanka M. Bose et al. reported that jaundice correlates best with CBDS as it has the highest sensitivity of 69% among other clinical parameters, but cholangitis is more specific with PPV reaching 100% (6). Menezes et al. confirmed that jaundice and ascending cholangitis are significant clinical factors in predicting CDL (19). A combination of cholangitis with other laboratory and radiological modalities increases the odds of harboring CBD calculi (20). A similar study conducted in Saudi Arabia showed the predictive value of raised ESR reflected the fact that most of the patients had either gallbladder or CBD stones with associated cholangitis and therefore a raised ESR (21).

Regarding the radiological parameters, one study showed a low sensitivity (35.7%) of sonography and (54.5%) for CBD dilatation as a predictor of CBDS, CBD diameter had a high negative predictive value 95.4%. In contrast, ERCP had a high sensitivity (96.0%) and specificity (99.1%) in the detection of CBDS hence being considered as the gold standard test, but it is not practical to perform it in every single patient (9). In the study conducted by Shashanka M. Bose et al, CBD dilation on ultrasonography demonstrated a sensitivity of (85%) and a negative predictive value of (93%), and a CBD diameter more than 7 mm had (84%) sensitivity and (82%) specificity, and they have reported that as the CBD diameter increases the probability of having CBDS increases as well. Similarly, in our study, dilated CBD diameter on ultrasound was suggestive for the presence of CBDS independently, reaching a sensitivity of 82% and a specificity of 49%. This is important, as abdominal ultrasonography is a non-invasive and cost-effective method compared to other radiological modalities. Our findings showed that visualization of CBD stones on US was the best predictor of CBDS and seen in 83 % of patients in choledocholithiasis group. Regarding

CBD stone detection on ultrasound, in that study, they had a high specificity of (97%) but the sensitivity was only (50%), which is similar to our findings suggesting that some stones, especially the small ones, can be overlooked (6).

**5. Strength and limitation of the study**

The strength points of our study are that we reviewed medical records of all patients who underwent ERCP at King Fahd University Hospital over the past 10 years for suspected CBDS and then we included only confirmed cases of CBDS and those who were found to have normal CBD to compare different variables between the two groups, given that the studied factors are readily available and hence are used in clinical practice. The limitations of our study are that it is a retrospective study, and the total number of the population studied was small, future cohort studies and a larger sample size are warranted. Moreover, the studied biochemical data were taken at admission and at discharge, further elaboration of the pattern of elevation of the liver function tests may be an area for future research. As an additional point for the radiological parameters, we were hoping to compare the sensitivity, specificity of the detection of CBD dilation among ultrasonography, ERCP and MRCP, but in the population studied, only a small number of patients had undergone the MRCP thus it was excluded from the analysis.

**6. Conclusions**

Visualization of the stones in the CBD on trans-abdominal ultrasonography was the best predictor of the presence of CBDS [adj OR 4.744, sensitivity =34%]. CBD diameter ≥7 mm on ultrasonography in cases that the patient did not undergo cholecystectomy and more than 1 cm in cases that the patient underwent cholecystectomy are suggestive of CBDS. In presence of either conditions, we suggest proceeding to more invasive and therapeutic procedures such as ERCP.

**Acknowledgments:**

The Authors would like to thank the medical interns of Imam Abdulrahman Bin Faisal University, College of medicine: Eiman A. Alkhalifa, Nesreen A. Alumair, Ethar A. Albasry, Bayan A. Alzahrani, Bayan A. Alsaif for their appreciated contribution in the data collection for the study, as well as the statistical department at King Fahd University Hospital (KFHU) for their help.

**Conflict of Interest:**

There is no conflict of interest to be declared.

**Authors' contributions:**

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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