

## Predictive factors for synchronous common bile duct stones in patients with cholelithiasis

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### Abstract

**Background:** To determine the predictive factors of synchronous common bile duct (CBD) stones, data from 878 consecutive patients who underwent cholecystectomy in a university clinic from June 1991 to June 1996 were retrospectively analyzed.

**Methods:** Based on clinical, biochemical, and ultrasonographic criteria, 194 patients were selected for ERCP, 180 preoperative and 14 postoperative.

**Results:** Cannulation of CBD was successful in 192 (99%) patients. Stones were identified in 62 (32%) patients and sphincterotomy was performed in 56 (90%). Duct clearance was achieved in 43 (77%) cases. There was a high predictive value for the presence of CBD stones in patients with cholangitis, present jaundice, and dilated CBD with evidence of stones on ultrasound (75%, 72%, and 67% respectively). A dilated CBD without stone on ultrasound and elevated liver enzymes had less than 40% positive predictive value. History of previous jaundice, pancreatitis, previously raised liver enzymes, and present pancreatitis was predictive in less than 20% of the cases. Univariate analyses revealed that clinical findings of cholangitis and obstructive jaundice, elevated liver enzymes (previous and present), and ultrasonographic findings of stones in a dilated CBD were significant positive predictors. Subanalysis of each elevated liver enzyme revealed that alanine transaminase, aspartate transaminase, alkaline phosphatase, and gamma glutamyl transpeptidase were significant predictors. Both elevated conjugated and total bilirubins were also significant predictors for CBD stones.

**Conclusion:** Multivariate logistic regression analysis on these significant predictors showed that cholangitis (odds ratio [OR]: 10.5), dilated CBD with evidence of stones on ultrasound (OR: 7.4), elevated aspartate transaminase (OR: 2.9), and conjugated bilirubin (OR: 5.3) were jointly significant. The likelihood of having stones in the duct without

any of these predictors was 7%, but 99% when all the predictors were positive.

**Key words:** Predictive factors — Synchronous common bile duct stones — Cholelithiasis

The introduction of endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy in the early 1970s changed the practice of biliary surgery [4, 13]. Endoscopic sphincterotomy (ES) was first introduced for removal of recurrent or retained stones after cholecystectomy [5]. However, its rapid success has expanded the indications. Endoscopic sphincterotomy with stone extraction became a well-established procedure in the management of choledocholithiasis in high-risk elderly patients in whom a noninflamed gallbladder might be left in situ [18]. Patients with cholangitis not responding to antibiotics and patients with severe gallstone pancreatitis not responding to conservative treatment have also become the candidates for ERCP and sphincterotomy during the acute illness [19].

In the last decade, laparoscopic cholecystectomy (LC) has gained widespread acceptance and become the new “gold standard” for the treatment of symptomatic gallbladder disease. Laparoscopic management of associated choledocholithiasis via a transcystic or transcholedochal route has also been advocated [1]. However, it remains a demanding approach that cannot be applied by the majority of surgeons. Technical difficulties and necessity of advanced skills to manage synchronous CBD stones laparoscopically have fueled the use of preoperative ERCP and sphincterotomy prior to LC—an approach which fits in well with the minimally invasive concept [14].

ES and duct clearance are successful in 90–95% of patients with an acceptable morbidity and mortality rate [15]. Most of the complications are self-limited pancreatitis. However, CBD stones are detected in only 25–50% of the

patients who undergo ERCP. Therefore, knowledge of reliable factors predictive of synchronous CBD stones is essential to avoid unnecessary ERCP and reduce avoidable morbidity and costs.

The aim of this study was to determine such factors and their reliability in predicting CBD stones.

## Patients and methods

Between July 1991 and July 1996, 878 consecutive patients underwent cholecystectomy (783 laparoscopic and 95 open), of which 194 were selected for either preoperative or postoperative ERCP.

Data collected prior to ERCP included age, sex, history of right hypochondrial pain, indication for procedure—previous or present elevated serum liver enzymes, clinical findings of cholangitis, jaundice, pancreatitis, dilated CBD over 6 mm with or without stones on ultrasound, serum level of each liver enzyme (aspartate transaminase [AST], alanine transaminase [ALT], alkaline phosphatase [ALP], gamma glutamyl transpeptidase [GGT], lactate dehydrogenase [LDH])—bilirubins, and ultrasonographic findings.

Age was categorized as young (<65) and old (65 and above). Biochemical analysis of blood was evaluated as abnormal when liver enzymes and bilirubin levels were elevated greater than two times normal. Elevated liver enzyme tests were considered present when any three of AST, ALT, ALP, GGT, and LDH were elevated.

ERCP was performed with an Olympus JFIT side-viewing duodenoscope under fluoroscopic control. If sphincterotomy was indicated, the bile duct was cannulated with a papillotome (Wilson-Cook Med., Inc., NC, USA); a combination of coagulation and cutting diathermy was used. Stones were extracted with the Dormia basket or balloon catheter. Cholecystectomy was done between 24 to 72 h after ERCP.

## Statistical analysis

All statistical analyses were performed with the SPSS for Windows version 6.0. In the preliminary analysis, univariate statistical methods were used to determine which factors were significantly related to the presence of CBD stones. The chi-square test with Yates' correction or Fisher's exact test was used for categorical variables;  $p < 0.05$  was considered significant.

All significant factors from the univariate analysis were subsequently included in the multivariate logistic regression procedure. The FORWARD automatic variable selection procedure was used in determining which of these variables were predictors of presence of CBD stones. Presence of CBD stones on ERCP was the dependent variable. Four of 194 patients with missing data were excluded from the analysis. The missing data was ultrasonographic evaluation of CBD in two and ERCP findings due to failure in cannulation in two.

## Results

There were 73 males (38%) and 121 females (62%). The average age was 52 (range 13–86) years. Cannulation of CBD was successful in 192 cases (99%). Cannulation failure occurred in two patients (1%) in whom the ampulla was located in a large diverticulum; they were excluded from the study.

Some 180 patients (93%) had preoperative ERCP and 14 (7%) had postoperative ERCP. The indication for postoperative ERCP was obstructive jaundice in six patients—retained stones were found in all of them. Elevated liver enzymes and serum amylase levels were the indications in another six patients—ERCP findings were normal in all. In the remaining two patients, incomplete clearance of CBD in open exploration required postoperative ERCP. Stone extraction was successful in these cases.

**Table 1.** Indications for endoscopic retrograde cholangiopancreatography and positive predictive values

Indication	Number of patients (%), <i>n</i> = 194	Positive predictive value (%)
Previous LFT <sup>a</sup> elevation	31 (16)	16
Previous pancreatitis	7 (4)	14
Previous jaundice	8 (4)	13
Present LFT <sup>a</sup> elevation	139 (72)	37
Present pancreatitis	31 (16)	19
Present jaundice	52 (27)	67
Cholangitis <sup>b</sup>	8 (4)	75
Dilated CBD <sup>c</sup> without stone on ultrasound	53 (27)	36
Dilated CBD <sup>c</sup> with stone on ultrasound	36 (19)	72

<sup>a</sup> Liver function test

<sup>b</sup> Jaundice with fever, right hypochondrial pain

<sup>c</sup> Common bile duct

Stones were found in 62 cases out of 192 (32%). Six patients with multiple large stones (>15 mm) in the CBD were referred to surgery for open CBD exploration without endoscopic sphincterotomy attempt during our early experience with interventional ERCP. Endoscopic sphincterotomy was performed in 56 patients (90%). Both wire-guided cannulation and pre-cut sphincterotomy techniques were employed to improve success rate. Stone retrieval was successful in 43 (77%) cases. Failure of stone extraction occurred in eight patients (14%) because of the large size of stones (mean: 18.3 mm, ranging from 15 to 23 mm). These eight patients underwent open exploration of CBD. Two patients who had single small stones (<5 mm) had only sphincterotomy and subsequently underwent LC. Three patients who had septic cholangitis underwent sphincterotomy, one of which also required stenting. The mean duration for diagnostic ERCP was 25 (SD: 16 min) and 42 (SD: 21.5 min) when sphincterotomy and stone extraction were performed.

Indications for ERCP and positive predictive values (PPV) for these predictors are shown in Table 1.

Complications included pancreatitis in seven cases (4%), all of which resolved spontaneously. Pancreatitis occurred following sphincterotomy in two and diagnostic ERCP in five. One patient (0.5%) had a retained stone basket which required surgery and duodenotomy. Two patients (1%) had minor bleeding that stopped spontaneously without the need for blood transfusion.

Univariate analysis of each set of pre-op ERCP data was carried out to assess its significance in predicting the presence of CBD stones (Table 2). Cholangitis, jaundice, past and present elevated liver enzymes, and ultrasonographic finding of CBD stones were predictors on univariate analysis even after using the Bonferroni-Holm method to adjust for multiple comparisons. Analysis of individual enzymes revealed that elevated AST, ALT, ALP, GGT, and raised bilirubins (conjugated and total) were significant predictors.

Multiple logistic regression analysis on these 11 variables showed that only cholangitis, dilated CBD over 6 mm with stone(s) on ultrasound, elevated AST, and conjugated bilirubin were jointly significant (Table 3). The probability of having stones in CBD is thus: log odds ratio (OR) =  $-2.62 + (2.26 \times \text{cholangitis}) + (2 \times \text{dilated CBD with stone})$

**Table 2.** Analysis of preoperative parameters for statistical significance by using chi-square or Fisher's exact test\*

Predictors	CBD <sup>a</sup> stone		Significance	
	Absent ( <i>n</i> = 130) <sup>b</sup>	Present ( <i>n</i> = 62)	$\chi^2$	<i>p</i>
Age (years)				
>65	41 (32)	29 (47)		
<65	89 (68)	33 (53)	3.574	0.06
Sex (F percent)	83 (63)	38 (61)	0.002	0.93
Past history				
Right upper quadrant pain	130 (100)	61 (98)		0.54*
Right upper quadrant pain radiating back	60 (46)	23 (37)	1.058	0.19
Indication				
Cholangitis	2 (2)	6 (10)		0.02*
Resolved pancreatitis	6 (5)	1 (2)		0.43*
Previous jaundice	7 (5)	1 (2)		0.44*
Previously elevated liver enzymes	26 (20)	5 (8)		0.04*
Present elevation of liver enzymes	88 (67)	52 (84)		0.02*
Present pancreatitis	25 (19)	6 (10)		0.14*
Present jaundice	17 (13)	35 (56)	37.826	0.01
CBD >6 mm without stone on ultrasound	34 (26)	19 (31)	0.331	0.56
CBD >6 mm with stone on ultrasound	10 (8)	26 (42)	31.189	0.01
Laboratory invest				
Aspartate transaminase	78 (60)	55 (89)		0.01*
Alanine transaminase	80 (62)	54 (87)		0.03*
Alkaline phosphatase	70 (54)	52 (84)		0.01*
Gamma glutamyl transpeptidase	102 (78)	54 (87)		0.05*
Lactate dehydrogenase	68 (54)	42 (68)	3.481	0.06
Conjugated bilirubin	28 (22)	42 (71)	41.678	0.01
Total bilirubin	22 (17)	38 (61)	36.425	0.01
Ultrasonography findings				
GB stone = 1	11 (9)	6 (11)		
>1	111 (87)	52 (90)		0.78*
GB st. size <1 cm	102 (84)	42 (81)		
>1 cm	19 (16)	10 (19)		0.66*

<sup>a</sup> CBD, common bile duct

<sup>b</sup> Values in parantheses are percentages

**Table 3.** Predicted odds ratio of having stones in the common bile duct based on the multivariate logistic regression model

Predictor	Odds ratio (OR)	95% confidence interval		<i>p</i> value
Cholangitis	10.5	1.55	71.79	0.02
Dilated common bile duct with stone on ultrasound	7.4	2.85	18.99	0.01
Elevated aspartate transaminase	2.9	1.25	6.88	0.01
Elevated conjugated bilirubin	5.3	2.35	11.83	0.01

on ultrasound) + (1.08 × elevated AST) + (1.66 × elevated conjugated bilirubin), in which, cholangitis = 1 if present or 0 if not; dilated CBD over 6 mm with stone on ultrasound = 1 if yes or 0 if not; elevated AST = 1 if yes or 0 if not; and elevated conjugated bilirubin = 1 if present and 0 if not.

## Discussion

CBD stones are present in 10–15% of patients undergoing cholecystectomy and the incidence rises to 30% in those over 80 years of age [6]. In the prelaparoscopic cholecystectomy era, the traditional management for CBD stones was to perform a choledochotomy and stone extraction. However, open CBD exploration is associated with significant morbidity and retained stone rate [5, 18]. Preoperative

ERCP and sphincterotomy were introduced to avoid the complications associated with open CBD exploration [11]. To date, the endoscopic approach has never been convincingly proven to be superior to open exploration [19, 22].

After widespread acceptance of LC, the management of CBD stones has regained renewed interest. Several strategies have emerged to manage synchronous CBD stones. The first strategy is to ignore them. But it has been shown that 55% of untreated CBD stones became symptomatic, and half had complications [12].

The second option is routine preoperative cholangiography and sphincterotomy if stones are present in a dilated duct. However, this approach is not cost-effective and routine ERCPs are not without danger. ERCP has a morbidity rate of 3–6.4% and a mortality rate of 0.05–0.1%, increasing to a morbidity rate of 5–10% and a mortality rate of 1–3.1% when sphincterotomy is performed [6]. In addition, it is

**Table 4.** Predicted probability of having stones in CBD based on the pattern of predictors present in any individual patient

Model	Cholangitis	Dilated CBD with stone on ultrasound <sup>a</sup>	Elevated aspartate transaminase	Elevated conjugated bilirubin	Predicted probability (%)
1	No	No	No	No	7
2	Yes	No	No	No	43
3	No	Yes	No	No	35
4	No	No	Yes	No	18
5	No	No	No	Yes	28
6	Yes	Yes	No	No	85
7	Yes	No	Yes	No	69
8	Yes	No	No	Yes	80
9	No	Yes	Yes	No	61
10	No	Yes	No	Yes	74
11	No	No	Yes	Yes	53
12	Yes	Yes	Yes	No	94
13	Yes	Yes	No	Yes	97
14	Yes	No	Yes	Yes	92
15	No	Yes	Yes	Yes	89
16	Yes	Yes	Yes	Yes	99

<sup>a</sup> CBD, common bile duct

expensive [7]. Therefore, routine use of preoperative ERCP cannot be recommended in all patients undergoing cholecystectomy.

The third strategy is to perform intraoperative cholangiogram and retrieve CBD stones laparoscopically. Intraoperative cholangiography is successful in 88% of patients with a positive predictive value of 63–92% [16]. This procedure also delineates the biliary anatomy and may prevent bile duct injury. Furthermore, complete treatment of biliary lithiasis in one operation may avoid the joint risk of two procedures (ERCP and LC) [17]. Although routine use of intraoperative cholangiography adds about 20 min to the LC, fluoroscopic cholangiogram can be completed in an average time of 6.9 min [2]. However, it has a false-positive rate ranging from 2.1 to 67%, which leads to unnecessary CBD exploration or conversion to open surgery [16].

The fourth strategy is preoperative ERCP in selected cases. Preoperative ERCP reduces the need for intraoperative cholangiography, avoids the need for most postlaparoscopic studies, and provides important information for the bile duct anatomy prior to LC. However, the significant difference in developing recurrent biliary symptoms following sphincterotomy (21%) compared to the biliary surgical group (6%) and high cost of ERCP should be kept in mind [8, 24].

Experience with selective preoperative ERCP and sphincterotomy prior to LC has been accumulating [3, 8–10, 20, 26]. Clinical, biochemical, and ultrasonographic evidence of stones has been utilized as criteria in patient selection for ERCP. Some studies reported that only the severity of patient's initial illness (acute cholangitis, persistent obstructive jaundice, and acute gallstone pancreatitis) had higher than 85% positive predictive value [21, 23, 25]. Elevated liver enzymes correlated well with duct calculi with a positive predictive value of 30–60% in other studies [9, 11]. Ultrasonographic finding of a dilated duct was predictive in 20–70% of the cases, whereas evidence of stones in a dilated duct on ultrasound was almost uniformly accurate [3, 20, 26].

Multivariate analysis in this study has identified cholangitis, dilated CBD over 6 mm with stone(s) on ultrasound,

elevated AST, and conjugated bilirubin as the main predictive parameters.

A combination of predictors increases the odds of having stones in the CBD. By applying the derived formula, likelihood of having stones in the duct can be estimated; thereby, the number of the unnecessary ERCPs can be reduced. According to the formula, probability of having stones in the duct without any of these predictors is 7% whereas it increases to 99% if all four predictors are present (Table 4).

This study has identified important predictors of synchronous CBD stones in patients who require cholecystectomy. Selective use of ERCP in these patients will ensure a high yield rate and thus improve cost-effectiveness. The small number of patients who are "false negatives", i.e., have associated CBD stones but also do not have any abnormal parameters, usually have small stones that are likely to pass spontaneously. If not, postoperative ERCP can deal with most of them.

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