Surg Endosc (1999) 13: 778–781

Surgical Endoscopy
Ultrasound and
Interventional Techniques

Proposed criteria for preoperative endoscopic retrograde cholangiography in candidates for laparoscopic cholecystectomy

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Received: 10 July 1998 Accepted: 18 September 1998

Abstract
Background: There has been a dramatic increase in the number of endoscopic retrograde cholangiograms (ERC) performed on patients who are candidates for laparoscopic cholecystectomy (LC). The majority of these procedures result in normal findings. This study is an attempt to determine useful clinical criteria and strategy for predicting the presence or absence of common bile duct stones (CBDS) and the need for ERC in patients who are candidates for LC.
Methods: The observational portion of this study explored laboratory and ultrasound data from 134 consecutive patients who had undergone preoperative ERC, followed by LC, over a 4-year period. The data were then analyzed by multivariate logistic regression to determine the best models for predicting the presence or absence of stones in the common bile duct. Models using gamma glutamyl transpeptidase (GGT), alkaline phophatase (AP), common bile duct diameter (CBDIA), and amylase (AMY) were then evaluated retrospectively in 36 additional patients (validation group).
Results: A model based on GGT and common bile duct diameter as positive predictors and amylase as a negative predictor correctly classified 78% of the patients in the validation group. This model resulted in a negative predictive value (NPV), positive predictive value (PPV), sensitivity, and specificity of 0.88, 0.68, 0.87, and 0.71, respectively. The model utilizing AP was almost as effective. This model resulted in a NPV, PPV, sensitivity, and specificity of 0.83, 0.67, 0.80, and 0.71, respectively.
Conclusions: Although a number of laboratory values and imaging techniques correlate with the presence or absence of CBDS, our study confirms that individually they have poor predictive value. Our data and models suggest that elevated serum amylase is a negative predictor for CBDS. Elevated GGT and/or AP with widened CBDIA and normal AMY strongly suggest the presence of CBDS and the need for preoperative ERC. Elevated GGT, AP, or widened CBDIA with elevated amylase, in the absence of clinical pancreatitis, may suggest that small stones have passed through the ampulla of Vater and that the CBD is generally cleared of stones.

Key words: Common bile duct stones — Endoscopic retrograde cholangiograms (ERC) — Laparoscopic cholecystectomy — Gallbladder

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Common bile duct stones (CBDS) occur in 8–15% of patients scheduled for cholecystectomy [22, 27, 29]. The clinical significance of CBDS and measures to determine their presence or absence have been reviewed extensively in the surgical literature over the past several decades with much controversy and little consensus. The issue has become more acute in the era of laparoscopic cholecystectomy (LC) because of the surgeon's desire to have the common bile duct (CBD) cleared of stones prior to the definitive procedure. This has led to a dramatic increase in the number of preoperative endoscopic retrograde cholangiograms (ERC) performed in the United States.

Recent reports suggest that 10% of patients undergoing LC meet refined criteria for preoperative ERC. About one-half to two-thirds of these patients will not have stones [10, 16, 23, 25, 34, 35, 41]. It is generally agreed that if liver enzymes are normal and the CBD diameter (CBDIA) is normal (5 mm diameter plus 1 mm per decade over 50 years of age), there is almost 100% certainty that CBDS are not present [30, 39, 42]. A number of investigators have initiated both prospective and retrospective studies in an attempt to establish criteria that will best predict the presence or absence of CBDS [1, 8, 9, 11, 13, 18, 20, 21, 28, 31, 32, 36, 37].

While we wish to avoid the problems of retained common bile duct stones, we also want to reduce the number of unnecessary preoperative ERC. Aside from their added advantage of anatomical clarification, ERC carry the potential for complications including pancreatitis, hemorrhage, per-

foration, cholangitis, and stenosis of the sphincter in 10% of cases [12, 14, 24]. Finally, there is the added expense of a very sophisticated invasive procedure done under sedation. This study is an attempt to refine criteria for preoperative ERC in patients who are candidates for laparoscopic cholecystectomy in order to reduce the number of unnecessary ERC.

Patients and methods

We performed a retrospective analysis of 134 consecutive patients who had undergone ERC prior to laparoscopic cholecystectomy in a small community hospital. We excluded from this study those patients who, in our opinion, had evidence of common duct obstruction and positive indications for common duct exploration such as ultrasound evidence of common bile duct stones, cholangitis, icterus, and fulminant pancreatitis as being outside the aims of this study. A total of 107 patients were available for study after we excluded all patients who had coexisting malignancies, were on anticonvulsants or enzyme inducers that markedly affect GGT levels, or were known alcoholics [38, 43]. Seventy-six patients had all variables available for analysis; these patients were used for model building.

We extracted the following data from the charts: age, sex, admission temperature, weight, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma glutamyl transpeptidase (GGT), bilirubin (BILI), amylase (AMY), lipase, current or recent medications, common bile duct diameter (CBDIA) as measured by ultrasonography, and the ERC findings of the presence or absence of common bile duct stones. All patients had documented cholelithasis and subsequently underwent laparoscopic cholecystectomy.

The data were analyzed with the logistic regression subroutine of NCSS version III (NCSS, Kayesville, UT, USA). Inspection of logit plots for the individual variables was undertaken to identify variables that were candidates for transformation; none were found. Those variables with univariate two-tailed p values < 0.25 were tested pairwise for interaction. No significant interactions were found between continuous variables.

We then proceeded with the intention of creating a clinically useful model that could be performed by the clinician with a minimum of mathematical calculations. Two such models were developed. The ability of these models to predict CBDS was evaluated retrospectively in a validation group of 36 patients. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and proportion of patients classified correctly by the model were used for model evaluation. Comparisons of groups utilized two-tailed t-tests for continuous data and Fisher's exact test for discrete data. Confidence intervals (95%) for proportions were constructed using the exact binomial distribution.

Table 1. Descriptive statistics

Variable	n	With stones[a]	Without stones[a]	p[b]
Age (yr)	107	57.9 (19.7)	53.8 (19.1)	.24
Males	44	28	16	.11
Females	63	29	34	
Weight (lb)	102	174.7 (42.6)	187.1 (51.1)	.19
AST (U/L)	107	219.3 (183.9)	178.8 (209.6)	.29
ALT (U/L)	107	236.8 (199.3)	201.3 (232.5)	.40
Alk. phos.	107	244.6 (152.5)	152.8 (90.9)	.0003
GGT (U/L)	107	540.4 (317.7)	298.2 (225.8)	<.0001
Bili. (mg/dL)	107	5.1 (7.2)	1.9 (2.2)	.002
Amylase (U/L)	81	189.2 (445.5)	1168.9 (1387.7)	<.0001
Lipase (U/L)	60	72.8 (152.2)	475.8 (1209.3)	.06
CBDIA (mm)	102	8.5 (4.1)	6.9 (2.2)	.017

AST, aspartate aminotransferase; ALT, alanine aminotransferase; Alk. phos., alkaline phosphatase; GGT, gamma glutamyl transpeptidase; Bili., total bilirubin; CBDIA, common bile duct diameter by ultrasonography

[a] Mean (standard deviation) except for figures for males and females, which are count data

[b] Unpaired two-tailed T-tests, except for sex vs stones, which is two-tailed Fisher's exact test

Table 2. Models for CBDS

	Multivariable logistic regression				
Model	Variable	n	Regression coefficient	χ^2	p value
Model 1[a]	AMY	76	–0.002	9.85	0.0017
	GGT		0.0042	9.51	0.002
	CBDIA		0.29	5.9	0.015
	Intercept		–3.15	8.03	0.0046
Model 2[b]	AMY	76	–0.0019	9.24	0.0024
	AP		0.0081	7.37	0.0067
	CBDIA		0.35	7.4	0.0065
	Intercept		–3.46	7.75	0.0054

[a] For model 1, the quantity (–3.15 + 0.0042 · GGT + 0.29 · CBDIA–0.002 · AMY) is calculated. If the value is ≥0, a CBDS is predicted; otherwise, the absence of a stone is predicted

[b] For model 2, the quantity (–3.46 + 0.0081 · AP + 0.35 · CBDIA – 0.0019 · AMY) is calculated. If the value is ≥0, a CBDS is predicted; otherwise, the absence of a stone is predicted

Results

A total of 107 patients were available for the observational portion of the study. Table 1 shows the descriptive statistics of those with and without stones. In comparing patients with and without stones, the following factors were shown to have highly significant differences: AP, GGT, BILI, AMY, and CBDIA as measured by ultrasonography. It can be seen in Table 1 that AMY levels were higher in patients without stones than those with CBDS. We proceeded to develop models in which AMY was used as a negative predictor. In this manner, we arrived at model 1 ($-3.15 + 0.0042 \cdot GGT + 0.29 \cdot CBDIA - 0.002 \cdot AMY$). If the value of the equation is ≥0, CBDS are predicted. If the value is <0, CBDS are not predicted. A second model using AP rather than GGT is nearly as effective. These two models are presented in Table 2.

There were 47 patients in the validation group, but only 36 with enough data to evaluate the two models. When tested against the validation group, model 1 resulted in NPV, PPV, sensitivity, and specificity of 0.88, 0.68, 0.87, and 0.71, respectively. Model 2 resulted in values of 0.83, 0.67, 0.80, and 0.71, respectively. The probability of a stone was found to be proportional to GGT, AP, and CBDIA and inversely proportional to AMY. Aspects of predictive performance for models 1 and 2 are presented in Table 3. Model 1 correctly classified 78% of the patients in the validation group, whereas model 2 correctly classified 75% of the patients.

Discussion

Our clinical observation that GGT is a sensitive predictor of CBDS was supported by our data and is not dealt with extensively in the literature [6, 7, 26, 40]. The biochemistry and the clinical significance are somewhat complicated and needs further study. There is a gender difference in the normal range of GGT and perhaps in response to CBD stones. AP is almost as sensitive at predicting stones as GGT. Because GGT is not always availabe in hospital liver

Table 3. Predictive performance parameters for models 1 and 2 in validation group[a]

Model	Sensitivity	Specificity	PPV	NPV	Proportion correct
Model 1	0.87 (0.6, 0.98)	0.71 (0.49, 0.89)	0.68 (0.43, 0.87)	0.88 (0.64, 0.99)	0.78 (0.61, 0.9)
Model 2	0.8 (0.52, 0.96)	0.71 (0.48, 0.89)	0.67 (0.41, 0.87)	0.83 (0.59, 0.96)	0.75 (0.58, 0.89)

PPV, positive predictive value; NPV, negative predictive value
[a] Point estimate of parameter (95% Confidence Interval for parameter)

profiles, we developed and tested our model using AP in its place.

Our finding that elevated serum amylase is a strongly negative predictor is probably a function of biliary sludge and/or small stones passing through the cystic duct, into the common duct, and then proceeding through the ampulla of Vater into the duodenum. Gardner et al., Acosta et al., and Kelly have all demonstrated migration of gallstones from the gallbladder into the duodenum [2–5, 15, 19]. As the stones pass through the ampulla, transient elevation of the serum amylase occurs. Larger stones, which become impacted in the duct above the ampulla of Vater, do not cause back pressure on the duct of Wirsung and hyperamylasemia.

Because of the association between CBDS and gallstone pancreatitis, it has often been assumed that hyperamylasemia is a positive predictor for stones in the CBD. Reiss et al. and Taylor et al. have both noted that a history of pancreatitis is not associated with CBDS [30, 37]. Hauer-Jensen et al. and Koo and Traverso found serum amylase to have poor sensitivity and poor predictive value for CBDS [17, 20]. Saltzstein et al. noted that "elevated amylase level actually lowered the predictability of common bile duct stones because of the large number of stones found in patients with normal serum or urine amylase levels" [33]. The data of Barkun et al. indicated that hyperamylasemia is associated with the absence of CBDS, but the authors did not elaborate on these finding [8].

We believe that our findings are unique in two ways. First, our data suggest that elevated serum amylase is a negative predictor of stones in the CBD. Second, the simplicity of our models, which use GGT and/or AP along with CBDIA as positive predictors, allows for its bedside use, with or without the use of a calculator. It appears that the models reflect the pathophysiology of CBDS and can be expressed in simple statements based on readily available information. If GGT, AP, or CBDIA are increased with normal serum amylase, CBDS are predicted and preoperative ERC is indicated. If GGT, AP, or CBDIA are increased, along with increased amylase, the preoperative ERC can be omitted and an operative cholangiogram can be performed in conjunction with LC.

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