Predictive Factors for Synchronous Common Bile Duct Stone in Patients with Symptomatic Cholelithiasis

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Abstract

Background : Laparoscopic cholecystectomy (LC) has become the treatment of choice for patients with symptomatic cholelithiasis. About 8-15 per cent of patients with symptomatic gallstones may bear associated common bile duct (CBD) stones, The management of choledocholithiasis in the laparoscopic era remain debatable. Although pre-operative endoscopic cholangiopancreatography (ERCP) is available and highly accurate in the detection of CBD stones, its routine use is controversial because of its inherent disadvantages.

Objective : The aim of this retrospective study was to generate an effective predictive model for bile duct stones detection by pre-operative ERCP.

Method : Twelve pre-operative clinical, biochemical and sonographic variables from 206 consecutive patients who underwent pre-operative ERCP with LC for gallstones with/without CBD stones from October 1998 to December 2000 were retrospectively analysed

Results :143 of the 206 patients with gallstones were found to have CBD stones. The mean age was 61 (20-93) yr old, and 55.9 per cent were female. Multivariate analysis showed a high predictive value for the presence of CBD stones in patients aged $\geq$ 55 yr old (Odd radio (OR) 1.03, 95% confidence interval (95% CI) 1.01-1.05), jaundice (OR 2.7, 95% CI 1.7-4.8), elevated alkaline phosphatase (OR 1.002, 95% CI 1.000-1.005), CBD dilatation on ultrasound (OR 3.8, 95% CI 1.8-8) and CBD stone on ultrasound.

Conclusion : The important clinical presentations and investigating could allow more appropriate use of pre-operative ERCP in patients who have symptomatic gallstones with a suspected CBD stone prior to cholecystectomy.

Key word : Predictive, Common Bile Duct Stone, Cholelithiasis, ERCP

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Laparoscopic cholecystectomy (LC) has become the treatment of choice for patients with symptomatic cholelithiasis. About 8-15 per cent of patients with symptomatic gallstones may bear associated common bile duct (CBD) stones, with a higher prevalence in older age groups[1]. The access of the CBD through laparoscopy is much more difficult than through open laparotomy[2-4]. Therefore, there is a need for pre-operative evaluation for the presence or absence of bile duct stones, so that proper access and operative plan can be designed. Currently, there are many techniques to document the presence of CBD stones. They consist of endoscopic retrograde cholangiography (ERC), endoscopic ultrasonography (EUS), and magnetic resonance cholangiography (MRC). The preference of each technique depends on the availability, feasibility and expertise of the individual institution.

The management of choledocholithiasis in the laparoscopic era remains debatable. Although pre-operative cholangiography such as ERCP is available and highly accurate in the detection of CBD stones, its routine use is controversial. This is due to its inherent costs and disadvantages, such as acute pancreatitis induced by ERCP.

The aim of this retrospective study was to generate an effective predictive model for bile duct stone detection by pre-operative ERCP, based on the patient's clinical presentation and investigation findings.

MATERIAL AND METHOD

A retrospective analysis study was carried out on 206 consecutive patients who underwent pre-operative ERC between October 1998 and December 2000 with definite evidence of presence (n = 143) or absence (n = 63) of CBD stones at ERCP. The following 12 pre-operative predictors which were age, sex, clinical presentations (jaundice, cholangitis and acute pancreatitis), liver function profiles (total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and gamma GT levels) and ultrasonographic findings (CBD diameter and stones) were recorded. Patients with associated hepatic diseases such as primary hepatic malignancy (hepatocellular carcinoma, cholangiocarcinoma), secondary hepatic malignancy, pancreatic tumor, liver abscess, known cirrhosis and alcoholic liver diseases were excluded.

Statistical analysis

The univariate association between the presence of CBD stones and their predictive factors were tested using the Pearson chi-square test with Yates' correction for binary factors and Unpaired *t*-test for ordinal or quantitative factors. For multivariate analysis, stepwise multiple logistic regression was used to identify factors that significantly predicted the presence of stones.

RESULTS

A total of 206 patients (91 men and 115 women) were retrospectively evaluated. Their predictive variables are shown in Table 1. One hundred and forty-three of the 206 patients with gallstones were found to have CBD stones. The mean age was 61 (20-93) years old. They were 10 years older than patients without CBD stones. The female gender in both groups

Table 1. Data of the 12 predictive factors in 206 patients with gallstones.

Factor (normal value)	CBD stones (n = 143)	%	Without CBD stones (n = 63)	%
Age (years)	60.6 ± 16.3 (20-93)		50 ± 16.9 (18-87)	
Female (no)	80	55.9	35	55.6
Jaundice	101	70.6	30	47.6
Cholangitis	47	32.9	7	11.1
Pancreatitis	18	12.6	9	14.3
Alkaline phosphatase (18-166 u/l)	338.1 ± 211.2		220 ± 132.6	
GGT (2-34 u/l)	540.6 ± 461.7		356.3 ± 427.1	
Total bilirubin (0.3-1.2)	5.9 ± 6.5		4.5 ± 4.6	
AST (3-30 u/l)	154.3 ± 162.6		160.6 ± 158.1	
ALT (2-40 u/l)	201 ± 176.2		176.8 ± 188.6	
CBD dilatation on U/S (> 8 mm)	84	58.7	13	20.6
CBD stone on U/S	45	31.5	0	0
Timing : LFT-ERCP (day)	9.6 ± 9.9		8.3 ± 8.1	

was 56 per cent. Jaundice and cholangitis were commonly found in the CBD stones groups but acute pancreatitis occurred almost as frequently in both groups. In the positive CBD stones group, the following abnormalities of liver function tests were found: elevated alkaline phosphatase more than twice, elevated gamma-glutamyl transpeptidase (GGT) more than 16 times, elevated total bilirubin more than 5 times, elevated aspartate aminotransferase (AST) more than 5 times, and elevated alanine aminotransferase (ALT) more than 5 times the normal value. Ultrasonographic findings, which demonstrated CBD stones, were found in 45 patients. CBD dilatation was considered when the diameter was greater than 8 mm with their gallbladder remaining *in situ*.

From the univariate analysis, seven of the 12 predictive factors were found to be statistically significant. They were, age more than 55 years, clinical jaundice and cholangitis, alkaline phosphatase and GGT levels, sonographic features of CBD stones and CBD dilatation. According to the multivariate analysis as shown in Table 2 and 3, the independent predictive variables for the presence of CBD stones were: age > 55 years old, jaundice, elevated alkaline phosphatase > 2 times the normal value, and CBD stones or dilatation on ultrasound.

DISCUSSION

The management of a symptomatic CBD stone is debatable. Millbourn et al showed that 55 per cent of patients with untreated CBD stones later presented with biliary related complications during a maximum follow-up of 13 years[5]. Other studies demonstrated significant complications from retained CBD stones on long-term follow-up[6-8]. Gibney EJ suggested that asymptomatic CBD stones can safely be left alone[9]. However, it is generally considered that leaving stones in the duct should be avoided and it can be potentially hazardous as complications may occur.

Several studies had tried to define the predictive criteria for diagnosis of CBD stones by assessing clinical, biochemical and ultrasonographic parameters with variable results.

Barkun et al generated a predictive model for selecting patients for pre-operative ERCP using logistic regression. Their best model for predicting bile duct stones at ERCP included following indepen-

Table 2. Statistical evaluation of the 12 parameters as predictors of CBD stones.

Factor	P univariate	P Multivariate	OR (95% CI)
Age > 55 years	< 0.001	0.004	1.03 (1.01-1.05)
Sex	NS	NS	
Jaundice	0.003	0.017	2.7 (1.7-4.8)
Cholangitis	0.002	NS	
Pancreatitis	NS	NS	
Alkaline phosphatase	< 0.001	0.033	1.002 (1.0-1.005)
GGT	0.023	NS	
Total bilirubin	NS	NS	
AST	NS	NS	
ALT	NS	NS	
CBD dilatation on U/S	< 0.001	< 0.001	3.8 (1.8-8)
CBD stone on U/S	< 0.001	< 0.001	

Table 3. Accuracy of ultrasonography in identifying CBD dilatation and CBD stone.

Ultrasonography	CBD dilatation (%)	CBD stone (%)
Sensitivity	58.7	31.5
Specificity	79.4	100
Positive predictive value (PPV)	85.6	100
Negative predictive value (NPV)	45.9	39.1

Table 4. Combined predictive factors.

Factor	Sensitivity	Specificity	PPV	NPV
Jaundice, CBD	40.6	84.1	85.3	38.4
Age, Jaundice	46.2	82.5	85.7	40.3
Age, Jaundice, ALP > 2	21.7	96.8	93.6	35.3
Age, Jaundice, CBD	30.8	95.2	93.6	37.7
Age, Jaundice, ALP > 2, CBD	15.4	98.4	95.7	33.9

dent predictors: age over 55 years, elevated bilirubin (over 30 μ mol/l), CBD dilatation and CBD stone seen on ultrasonography(2).

In the present study, the clinical parameters which were found to be statistically significantly helpful as predictors of CBD stone in-patients with symptomatic cholelithiasis were: age > 55 years, jaundice, elevated alkaline phosphatase, presence of CBD stones or dilatation on ultrasonography. Only jaundice (OR = 2.7, 95% CI = 1.7-4.8), CBD dilatation (OR = 3.8, 95% CI = 1.8-8) and CBD stones were found to be powerful predictive factors. The probability of finding CBD stones at ERCP ranged from 20 per cent (when none of these predictors were present) to 96 per cent (when all the four predictors were present).

In the univariate analysis, factors that were found significant as helpful predictors were jaundice and cholangitis. However, cholangitis was not found to be significant in the multivariate analysis. There may be different clinical presentations of cholangitis, while most cases often have jaundice, some may not.

In the present study, pancreatitis was not found to be significant in either the univariate or the multivariate analysis. This is in accordance with other studies, which explained that patients with gallstone pancreatitis are likely to have passed the stone spontaneously prior to the time of evaluation(10-12).

Other studies have found biochemical parameters as being useful for predicting the presence of CBD stones, but these results were highly variable. Prat F et al used endoscopic sonography to detect the presence of CBD stones, they found elevated GGT above 7 times of normal as an independent predictive factor for the presence CBD stones(13), while elevated GGT was not statistically helpful by multivariate analysis in the present study.

While persistent jaundice was found to be a significant predictor in most studies(14), serum bilirubin concentration was not found to be statistically significant in some studies, especially in the multivariate analysis(15,16). This may be due to the presence of clinical jaundice which signifies the higher level of bilirubin to be included as a factor, while patients with low level hyperbilirubinemia may not be included as patients with clinical jaundice.

Menezes et al showed elevated transaminase levels > 2xN were significant predictors(15). In the present study, the elevated serum transaminase concentration was not found to be significant predictors for CBD stones. In gallstone patients with or without CBD stones, the transaminase level can be elevated by many other factors e.g. drug induced hepatotoxicity, chronic hepatitis B and C which are common in Thai populations. Other reasons that may also interfere with the analysis are, the spontaneous passing of a CBD stone may give transient spike of transaminase and the delayed evaluation of CBD stone by ERCP (as shown in Table 1).

In the present study, ultrasonographic abnormality was found to be a positive predictor of CBD stones. However, the accuracy of ultrasonography in identifying CBD stone is low, as the possibility of direct visualizing a CBD stone was only 32 per cent. Apart from that, the ultrasonic evidence of CBD dilatation is only an indirect sign which had a sensitivity of 59 per cent. The main advantage of ultrasound is the high positive predictive value (PPV) of direct stone visualization. In the present study, the cases that were found to have CBD stone from ultrasonography were invariably confirmed by ERCP (PPV 100%).

Abboud et al presented a meta-analysis of 22 articles in the English literature, which showed

isolated single clinical predictor alone, cannot accurately predict CBD stone prior to cholecystectomy. The most powerful positive predictor came from the combination of several predictors, which included cholangitis, jaundice, CBD stones or dilatation on sonography. Patients with any one of these indicators had at least seven to ten times the odds of CBD stones when compared with patients lacking any of the indicators. On the other hand, the low likelihood ratio of these predictors suggest that the absence of any of them only provided very weak information[14]. In the present study, combinations of two predictive factors such as 1) age and jaundice or 2) jaundice and CBD dilatation have PPV 85 per cent. When the combination of 3 or 4 predictors were used, PPV was about 95 per cent (as shown in Table 4).

SUMMARY

Age, jaundice, elevated alkaline phosphatase, CBD dilatation or stones on ultrasonography were found to be helpful predictors which is similar to other studies but elevated GGT and cholangitis were not helpful predictors in the present study. The combinations of several predictive factors was the increased power of these predictors to predict the presence of CBD stone(s).

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ดัชนีบ่งชี้การพบนิ่วในท่อน้ำดีของผู้ป่วยที่มีอาการนิ่วในถุงน้ำดี

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การผ่าตัดถุงน้ำดีด้วยการส่องกล้องผ่านผนังหน้าท้อง ในปัจจุบันถือเป็นการรักษาที่เหมาะสมในผู้ป่วยที่มีอาการนิ่วในถุงน้ำดี ประมาณร้อยละ 8-15 ของผู้ป่วยกลุ่มนี้จะมีนิ่วในท่อน้ำดีร่วมด้วย ซึ่งการรักษานิ่วในท่อน้ำดีในปัจจุบันยังมีหลายวิธี อย่างไรก็ตามการฉีดสีดูท่อน้ำดีก่อนผ่าตัดในสถานที่สามารถทำได้ พบว่ามีความแม่นยำในการวินิจฉัยนิ่วในท่อน้ำดีและเป็นวิธีให้การรักษาไปด้วย แต่การทำหัตถการดังกล่าวทุกรายก่อนผ่าตัดนิ่วในถุงน้ำดีนั้นยังมีข้อมูลที่ขัดแย้งอยู่ถึงผลเสียและประโยชน์ที่จะได้รับ จึงได้ทำการศึกษาหาดัชนีบ่งชี้นิ่วในท่อน้ำดี ในผู้ป่วยที่มีอาการนิ่วในถุงน้ำดี เพื่อใช้ในการพิจารณาว่าผู้ป่วยรายใดควรทำ endoscope retrograde cholangiopancreatography (ERCP) ก่อนการผ่าตัด

รายงานนี้เป็นการศึกษาย้อนหลังผู้ป่วยที่มีอาการนิ่วในถุงน้ำดี ซึ่งได้รับการทำ ERCP ก่อนการผ่าตัดส่องกล้องผ่านผนังหน้าท้องทุกราย ที่เข้ามารับการรักษาในคณะแพทยศาสตร์ศิริราชพยาบาล ระยะเวลาตั้งแต่ตุลาคม 2541 ถึง ธันวาคม 2543 โดยศึกษาดัชนีทางคลินิก การตรวจทางห้องปฏิบัติการและภาพรังสีอัลตราซาวด์ พบว่าผู้ป่วยที่มีอาการนิ่วในถุงน้ำดีจำนวน 206 ราย พบมีนิ่วในท่อน้ำดีร่วมด้วย 143 ราย มีอายุเฉลี่ย 61 ปี (20-93 ปี) และเป็นผู้ป่วยหญิงร้อยละ 55.9 ผลการวิเคราะห์ทางสถิติแสดงให้เห็นว่าดัชนีที่บ่งชี้การพบนิ่วในท่อน้ำดี ได้แก่ อายุมากกว่า 55 ปี (OR 1.03, 95% CI 1.01-1.05) ภาวะดีซ่าน (OR 2.7,95% CI 1.7-4.8) ระดับอัลคาไลน์ ฟอสฟาเตสที่สูงขึ้นกว่าค่าปกติ (OR 1.002, 95% CI 1.000-1.005) และการตรวจภาพรังสีอัตราซาวนด์พบ ท่อน้ำดีขยายตัว (OR 3.8,95% CI 1.8-8) หรือพบนิ่วในท่อน้ำดี

การใช้ดัชนีทางคลินิก และการตรวจทางห้องปฏิบัติการเบื้องต้น เช่น ระดับอัลคาไลน์ ฟอสฟาเตส และภาพรังสีอัลตราซาวนด์ สามารถบ่งชี้โอกาสพบนิ่วในท่อน้ำดี ซึ่งจะช่วยในการเลือกผู้ป่วยที่มีอาการนิ่วในถุงน้ำดี ว่ารายใดเหมาะสมที่จะทำ ERCP ก่อนการผ่าตัด เพื่อให้ได้ประโยชน์สูงสุด

คำสำคัญ : ดัชนี, นิ่วในถุงน้ำดี, นิ่วในท่อน้ำดี, การส่องกล้องฉีดสีท่อน้ำดีและตับอ่อน

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