Predictive Factors for Choledocholithiasis in Symptomatic Gallstone Patients

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**Background:** Complications of common bile duct stones (choledocholithiasis) can vary from simple biliary colic to life-threatening conditions. Approximately 10-25% of symptomatic gallstone patients may be associated with common bile duct stone (CBDS) at the time of diagnosis. Endoscopic retrograde cholangiopancreatography (ERCP) is the gold standard for diagnosis and treatment of CBDS, but this procedure is invasive and has high morbidity and mortality rate. Moreover, routine preoperative ERCP is not cost-effective.

**Objective:** This study aimed to determine the predictive factors for predicting CBDS in symptomatic gallstone patients.

**Material and Method:** Between March 2008 and February 2011, 149 symptomatic gallstone patients who underwent preoperative ERCP or intraoperative cholangiography (IOC) during laparoscopic cholecystectomy at Her Royal Highness Princess Mahachakri Sirindorn Medical Center (MSMC) were evaluated by clinical presentations, biochemical blood test and transabdominal ultrasonography. The preoperative predictive factors for choledocholithiasis were determined by univariate and multivariate analysis.

**Results:** Age more than 55 years, history of jaundice, history of cholangitis, total bilirubin >2.0 mg/dL, Aspartate aminotransferase >2 times the normal value, Alanine aminotransferase >3 times the normal value, Alkaline phosphatase >300 U/L, Gamma glutamyltranspeptidase >90 U/L, sized of CBD >8 mm and visualized CBD stones by ultrasonography were found to be associated with CBD stones by univariate analysis. For multivariate analysis, history of cholangitis (p-value 0.027), sized of CBD >8 mm (p-value 0.003) and detected CBD stones by ultrasonography (p-value 0.000) were found to be predictive factors for choledocholithiasis.

**Conclusion:** This study presented that the helpful preoperative predictive factors for choledocholithiasis were history of cholangitis, dilatation of CBD >8 mm and visualized CBD stone by ultrasonography.

**Keywords:** Predictive factors, Choledocholithiasis, Gall stone, Common bile duct stone

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Symptomatic gallstone is one of the most common diseases in surgical patients. Approximately 10-25% of symptomatic gallstone patients may have stones in common bile duct (choledocholithiasis) at the time of diagnosis(1,2). Common bile duct stones (CBDS) cause obstructive jaundice and cholangitis. Complications of common bile duct stones can vary from biliary colic to life-threatening conditions such as suppurative cholangitis and sepsis. Accurate preoperative prediction of choledocholithiasis is necessary to decrease operative risk and help surgeons to decide type of surgery. Clinical evaluation, biochemical blood tests and transabdominal ultrasonography are routinely used as preoperative workup for predicting choledocholithiasis. However, these approaches are not accurate to establish a firm diagnosis. Magnetic resonance cholangiopancreatography (MRCP) is a noninvasive procedure with no associated morbidity and mortality that has become the gold standard in diagnosing CBDS. However, MRCP is an expensive, requires expertise for interpretation and may miss stones less than 5 mm in diameter. Endoscopic retrograde cholangiopancreatography (ERCP) is the gold standard for diagnosing and treating CBDS; however, it is an invasive procedure with high morbidity and mortality rate such as duodenal perforation, acute cholangitis and acute pancreatitis. Preoperative ERCP may be not recommended routinely due to its high negative finding, expensive and had significant morbidity. The development of predictive factor for CBDS, based on the patient’s clinical, biochemical blood test and
transabdominal ultrasonography could allow a more accuracy of preoperative diagnosed CBDS. Therefore, the aim of this study was to determine the predictive factors for predicting CBDS in symptomatic gallstone patients.

Material and Method

A prospective analysis study of 149 symptomatic gallstone patients who underwent preoperative ERCP before laparoscopic cholecystectomy or intraoperative cholangiography (IOC) during laparoscopic cholecystectomy from March 2008 to February 2011 at Her Royal Highness Princess Mahachakri Sirindorn Medical Center (MSMC) was evaluated. The preoperative predictive factors which were age, sex, clinical presentations (history of cholangitis, history of jaundice, history of pancreatitis), liver biochemical test (serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyltranspeptidase (GGT)) and transabdominal ultrasonography (number of gallstone, sized of CBD, CBD stones) were recorded. Symptomatic gallstone patients with associated liver cirrhosis, liver abscess, alcoholic liver disease, hepatic malignancy (primary or secondary) and periampullary carcinoma were excluded. The diagnosis of cholangitis was established by the presence of Charcot’s triad (fever, abdominal pain and jaundice). The diagnosis of pancreatitis was established by the presence of severe upper abdominal pain radiating to back. Criteria used to define abnormal biochemical blood tests includes total bilirubin >1.0 mg/dL, serum AST >37 U/L, serum ALT >37 U/L, serum ALP >128 U/L and GGT >31 U/L. The transabdominal ultrasonography was performed by three radiologists.

Statistical analysis was performed using Chi-square test with Yates’ continuity correction for univariate analysis between the presence of CBDS and the predictive factors. Multiple logistic regression test was used to identify predictive factors CBDS for multivariate analysis. The p-value <0.05 was considered statistically significant.

Results

A total of 149 symptomatic gallstones patients who underwent preoperative ERCP before laparoscopic cholecystectomy or intraoperative cholangiography (IOC) during laparoscopic cholecystectomy between March 2008 and February 2011 were evaluated. Preoperative ERCP was 98 patients (65.78%) and intraoperative cholangiography (IOC) was 51 patients (34.22%). CBD stones were found in 48 out of 149 patients (32.21%). There were 58 males (38.9%) and 91 female (61.1%). The mean age was 57.25±14.53 (20-90) years old. History of jaundice and cholangitis were more commonly presented in CBDS patients than in without CBDS patients. In contrast, the history of pancreatitis was rarely found in both groups.

For the biochemical blood test, the CBDs patients with total bilirubin ≥2.0 mg/dL were 37.5% whereas the without CBDS patients were 4.95%. For liver enzyme, the AST >2 times the normal value and ALT >3 times the normal value in CBDs patients were 45.83% and 37.5% whereas those in without CBDS patients were 5.94% and 8.91%, respectively. Alkaline phosphatase (ALP) and Gamma glutamyltranspeptidase (GGT) are the key parameters in CBDS. The data showed that the CBDS patients with ALP >300 U/L and GGT >90 U/L were 35.41% and 79.16% while the without CBDS patients were in only 2.97% and 23.76%, respectively.

For ultrasonographic finding, multiple gallstones were found 75% in CBDS patients and 69.30% in without CBDS patients. CBD dilatation ≥8 mm which is a meaningful parameter to define CBD obstruction was found 85.41% in CBDs patients while was found only 12.87% in without CBDS patients. CBD stones detected by ultrasonography, were found 77.08% in CBDS patients and 3.96% in without CBDS patients.

For univariate analysis, three predictive factors of biochemical blood test and two predictive factors of ultrasonographic finding demonstrated to be statistically significant. They were age >55 years, history of jaundice, history of cholangitis, total bilirubin ≥2.0 mg/dL, AST >2 times the normal value, ALT >3 times the normal value, ALP >300 U/L, Gamma GT ≥90 U/L, sized of CBD ≥8 mm and ultrasonographic features of CBD stones. The individual significant factors in CBDS diagnosis revealed univariate analysis were analyzed with multivariable analysis. They showed that three factors were significant for predicting CBDS as follows: history of cholangitis (p-value 0.027), sized of CBD ≥8 mm (p-value 0.003) and detected CBD stones by ultrasonography (p-value 0.000).

According to the multivariable analysis, diagnostic test of the individual predictive factors for CBDS was shown in Table 3. The history of cholangitis was the highest in specificity (97.02%) whereas sized of CBD ≥8 mm was the highest in sensitivity (85.41%) and in NPV (92.63%). And the detected CBD stones by
Table 1. Baseline characteristics of patient (n = 149)

<table>
<thead>
<tr>
<th>Predictive factors</th>
<th>GS without CBD stone (n = 101)</th>
<th>GS with CBD stone (n = 48)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>34/67</td>
<td>24/24</td>
<td>0.056</td>
</tr>
<tr>
<td>Age ≥55</td>
<td>45 (44.55%)</td>
<td>36 (75%)</td>
<td>0.001*</td>
</tr>
<tr>
<td>History of jaundice</td>
<td>8 (7.92%)</td>
<td>16 (33.33%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>History of cholangitis</td>
<td>3 (2.97%)</td>
<td>20 (41.67%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>History of pancreatitis</td>
<td>4 (3.96%)</td>
<td>2 (4.16%)</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin &gt;2.0 mg/dL</td>
<td>5 (4.95%)</td>
<td>18 (37.5%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Aspartate aminotransferase &gt;2x normal</td>
<td>6 (5.94%)</td>
<td>22 (45.83%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Alkaline phosphatase &gt;300 U/L</td>
<td>3 (2.97%)</td>
<td>17 (35.41%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Gamma GT &gt;90 U/L</td>
<td>24 (23.76%)</td>
<td>38 (79.16%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Multiple gall stones</td>
<td>70 (69.30%)</td>
<td>36 (75%)</td>
<td>0.474</td>
</tr>
<tr>
<td>Sized of CBD &gt;8 mm</td>
<td>13 (12.87%)</td>
<td>41 (85.41%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>CBD stone by U/S</td>
<td>4 (3.96%)</td>
<td>37 (77.08%)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

* = statistically significant (p-value <0.05)

Table 2. Predictive factors for CBD stones

<table>
<thead>
<tr>
<th>Predictive factors</th>
<th>Adjusted odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥55</td>
<td>3.14 (0.46-21.08)</td>
<td>0.238</td>
</tr>
<tr>
<td>History of jaundice</td>
<td>0.23 (0.01-4.7)</td>
<td>0.344</td>
</tr>
<tr>
<td>History of cholangitis</td>
<td>15.27 (1.36-170.32)</td>
<td>0.027*</td>
</tr>
<tr>
<td>Total bilirubin &gt;2.0 mg/dL</td>
<td>8.61 (0.35-209)</td>
<td>0.186</td>
</tr>
<tr>
<td>Aspartate aminotransferase &gt;2x normal</td>
<td>0.69 (0.03-5.68)</td>
<td>0.806</td>
</tr>
<tr>
<td>Alkaline phosphatase &gt;300 U/L</td>
<td>1.73 (0.1-28.93)</td>
<td>0.702</td>
</tr>
<tr>
<td>Gamma GT &gt;90 U/L</td>
<td>0.45 (0.03-5.68)</td>
<td>0.539</td>
</tr>
<tr>
<td>Sized of CBD &gt;8 mm</td>
<td>17.50 (2.70-113.24)</td>
<td>0.003*</td>
</tr>
<tr>
<td>CBD stone by U/S</td>
<td>69.61 (10.49-461.94)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

* = statistically significant (p-value <0.05)

Table 3. Diagnostic test of predictive factors for CBD stones

<table>
<thead>
<tr>
<th>Predictive factor</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of cholangitis</td>
<td>41.67%</td>
<td>97.02%</td>
<td>86.95%</td>
<td>77.77%</td>
<td>79.19%</td>
</tr>
<tr>
<td>Sized of CBD &gt;8 mm</td>
<td>85.41%</td>
<td>87.13%</td>
<td>75.92%</td>
<td>92.63%</td>
<td>86.57%</td>
</tr>
<tr>
<td>CBD stone by U/S</td>
<td>77.08%</td>
<td>96.04%</td>
<td>90.24%</td>
<td>89.81%</td>
<td>96.64%</td>
</tr>
</tbody>
</table>

PPV = positive predictive value; NPV = negative predictive value

ultrasonography were the highest in PPV (90.24%) and accuracy (96.64%).

Discussion

Gallstones are the common disease. Laparoscopic cholecystectomy (LC) has become a standard treatment for symptomatic gallstone patients. Approximately 10-25% of symptomatic gallstone patients have CBDS(1-2). CBDS may be associated with severe complication such as acute cholangitis and
pancreatitis. ERCP is invasive procedure and high morbidity and mortality rate. MRCP is an expensive and requires expertise for interpretation. Therefore preoperative ERCP and MRCP routinely use is not cost-effectiveness. There have been several studies which defined the preoperative predictive factor for CBDS by assessing clinical presentation, biochemical blood test and transabdominal ultrasonography. However, the results of these studies were inconclusive.

In clinical presentation parameters, Barkun et al (3), Charatcharoenwitthaya et al (4) and Vijitpornkul et al (5) reported that age >55 years was a predictive factor for CBDS. In our study, age >55 years was helpful predictor for CBDS in the univariate analysis. However, it wasn’t statistically significant in the multivariate analysis. In addition, history of jaundice and history of cholangitis were significant for CBDS in the univariate analysis but only history of cholangitis was found to be significant in the multivariate analysis. These might be cause of different clinical presentation of cholangitis, while almost half cases may not have jaundice. History of pancreatitis was found to be insignificant in neither the univariate nor the multivariate analysis. This is in accordance with other clinical series, which explained that almost patients with gallstone pancreatitis are likely to have spontaneously passed the stone across the sphincter of Oddi prior to the time of evaluation (6, 7).

Several studies demonstrated that the biochemical blood test was helpful for predicting CBDS. However these results were highly different. Sgourakis et al (8) reported that direct bilirubin > 2 times the normal value, AST > 2 times the normal value, ALP > 2 times the normal value and CBD dilated > 1 cm were predictive factor for CBDS. Peng et al (9) showed that GGT > 90 U/L was highest specificity, PPV and NPV for the predictor CBDS than other liver function test. Santucci et al (10) demonstrated that ALP ≥ 300 IU/L, ALT > 40 IU/L and CBD dilated > 8 mm were variables for CBDS diagnosis. Lakatos et al (11) reported that hyperbilirubinemia ≥ 2 times the normal value, elevated AST/ALT > 50%, elevated GGT/ALP > 50%, acute pancreatitis, jaundice, CBD stones and CBD dilated > 8 mm were predictive factor for CBDS. Prat et al (12) demonstrated that GGT > 7 times the normal value, CBD dilated > 8 mm and CBD stones were variables for CBDS diagnosis. In this study, total bilirubin ≥ 2.0 mg/dL represented jaundice, AST ≥ 2 times the normal value, ALT ≥ 3 times the normal value represented liver injury and ALP ≥ 300 U/L, GGT ≥ 90 U/L represented bile duct obstruction, were statistically significant as helpful predictors for CBDS in the univariate analysis. However no any biochemical test was found to be significant in the multivariate analysis.

For ultrasonographic finding, the review literatures showed that CBD dilatation and detected CBD stone by ultrasonography were statistically significant as helpful predictive factors for CBDS both the univariate and the multivariate analysis. This study also demonstrated similar results. Criteria of CBD dilatation was different each study. Most studies used CBD dilated > 8 mm which was radiologic criteria for CBD obstruction. Some studies such as Vijitpornkul et al (5) and Sgourakis et al (8) used CBD dilated > 1 cm. On the contrary, Barkun et al (3), Alponat et al (13) and Notash et al (14) used CBD dilated > 6 mm for predicting CBDS. Vijitpornkul et al (5) reported that multiple gallstones were predictive factors for CBDS but other studies include this study conversely resulted.

In this study, diagnostic test of sized of CBD ≥ 8 mm for predicting CBDS is the highest in sensitivity and NPV therefore it should be appropriately for screening CBDS. CBD dilatation implies CBD obstruction which may be indirect sign for CBDS. Diagnostic test of the detected CBD stone by ultrasonography is high in specificity, PPV and accuracy because it is direct CBD stone visualization. However it isn’t the highest in sensitivity due to operator dependence. Diagnostic test of history of cholangitis for predicting CBDS is low in sensitivity but high in specificity. It is because the most of symptomatic patients with CBDS will present with history of cholangitis.

The limitations of this study, history of cholangitis vary in diagnosis by the physician’s finding and the results of ultrasonography are different due to operator dependence. These factors are effect to predict choledocholithiasis in symptomatic gallstone patients. We recommend study in large population for decreasing variation result.

In conclusion, this study present that the helpful preoperative predictive factors for choledocholithiasis are history of cholangitis, dilatation of CBD ≥ 8 mm and visualized CBD stone by ultrasonography. Sized of CBD ≥ 8 mm is the highest in sensitivity, history of cholangitis is the highest in specificity and visualized CBD stone by ultrasonography is the highest in accuracy.

What is already known on this topic?

There have been several studies which defined the preoperative predictive factor for CBDS by
assessing clinical presentation, biochemical blood test and transabdominal ultrasonography with highly different results.

What this study adds?

The preoperative clinical prediction for choledocholithiasis is in symptomatic gallstone patients are history of cholangitis, dilatation of CBD >8 mm and visualized CBD stone by ultrasonography. Therefore, preoperative ERCP recommend setting up in gallstone patients who have these predictive factors.

Acknowledgements

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Potential conflicts of interest

None.

References

ปัจจัยที่มีผลต่อการหาทางเดินในหนอนที่ไม่สามารถมองเห็นในกลุ่มตัว

วิชิต วิริยาจินต ธรรมนูญ รุทธาทิพย์

ภูมิหลัง: การพบการกลับคืนในหนอนนั้นเป็นปัญหาที่คล้ายคลึงกันในหลายๆ ประเทศ เช่นการรักษาหนอนดินตัวป่วยเป็นโรคศรีษะ ผู้ป่วยมีอายุตั้งแต่ 10-25% ของผู้ป่วยที่วัยเจริญน้ำหนักในกลุ่มนี้จะมีในกลุ่มนี้ที่มีติดต่อกัน ซึ่งการสงผลของการดินตัวไม่ได้เป็นปัจจัยที่มีความสุข แต่มีภาวะที่มีอาการที่สูง ซึ่งไม่เหมาะสมในการทำส่งผลดีต่อการดินตัวที่ติดต่อกันในกลุ่มนี้ไม่ได้

วัตถุประสงค์: เพื่อศึกษาปัจจัยทางคลินิก การตรวจทางแผนภูมิ และการตรวจเส้นทางความสูงของทอง เพื่อใช้ในการวางแผนว่านอนในหนอนที่มีภูมิปัญญา

วัสดุและวิธีวิจัย: ทำการศึกษาผู้ป่วยที่มีการดินตัว 149 ราย ที่ได้รับการดูแลดินตัวต่อก่อนการบาดเจ็บ หรือได้รับการดูแลดินตัวต่อ ระหว่างการบาดเจ็บ กรุณาใช้โทรศัพท์หรืออินเทอร์เน็ต ซื่อที่ที่เดียวกัน ตั้งแต่ พ.ศ. 2551-2554 จากกลุ่มปัจจัยต่างๆ ที่เกี่ยวข้อง เพื่อทำการวิเคราะห์ในหนอนที่ไม่ได้ใช้การวิเคราะห์สถิติที่ univariate และ multivariate

ผลการศึกษา: พบว่าการรักษาผู้ป่วย 55 ปี ที่มีการดินตัวต่อก่อน รักษาได้ดีขึ้นในหนอนที่ คุณค่าของแผนภูมิ 2 บาทของสูญ คุณค่าของแผนภูมิ เอกซ์ที่ มากกว่า 2 เท่าของสูญ คุณค่าของแผนภูมิ 3 เท่าของสูญ คุณค่าของแผนภูมิ มากกว่า 300 คุณค่าของแผนภูมิ ค่าที่สูงที่สุด มากกว่า 90 คุณค่าของแผนภูมิ ขนาดของหนอนที่มากกว่า 8 มิลลิเมตร การดินตัวจากการตรวจสอบเส้นทางความสูงของทอง จะเกิดขึ้นในหนอนที่ไม่ได้

ตามวิเคราะห์ multivariate จะพบว่าการดินตัวในหนอนที่ (p-value 0.027) ขนาดของหนอนที่มากกว่า 8 มิลลิเมตร (p-value 0.003) และหนอนที่ไม่ได้จากการตรวจสอบเส้นทางความสูงของทอง (p-value 0.000) ที่เป็นปัจจัยในการวางแผนในหนอนที่

สรุป: ปัจจัยทางคลินิกที่มีผลต่อการดินตัวในหนอนที่ไม่ได้เป็นปัจจัยที่มีต่อการดินตัวกันในหนอนที่ การมีติดต่อกันมากกว่า 8 มิลลิเมตร และหนอนที่ไม่ได้จากการตรวจสอบเส้นทางความสูงของทอง ดังนั้นการส่งผลดีดินตัวกันไม่ได้การดินตัวกัน

แนวโน้มควรจะมีการศึกษาในกลุ่มนี้ที่ปัจจัยต่อเนื่อง