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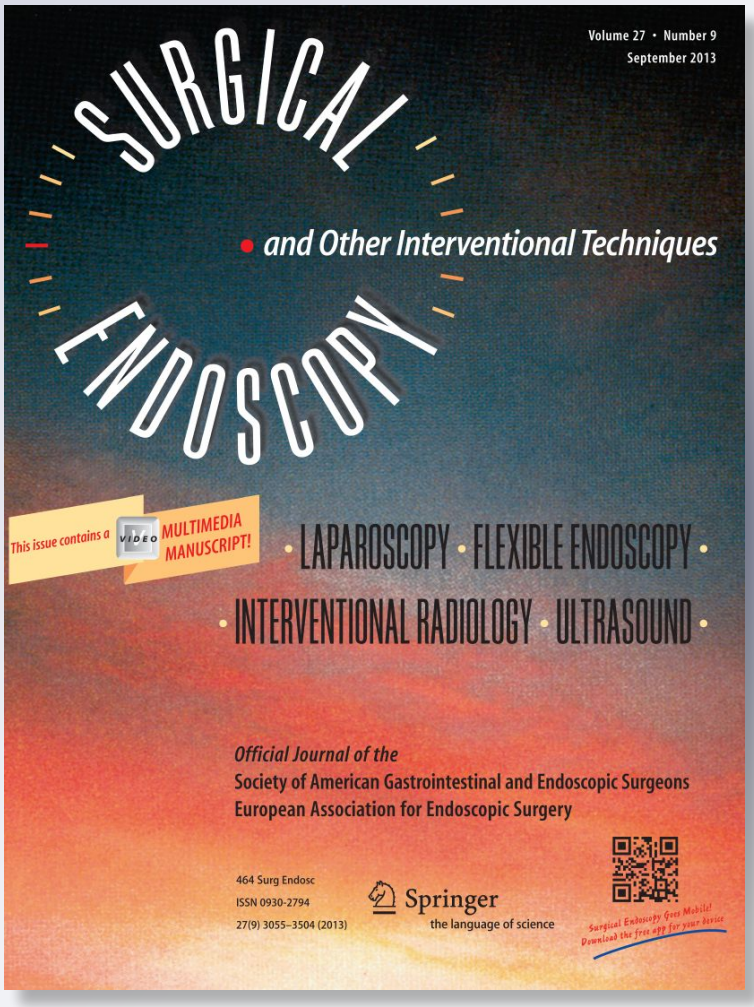
Surgical Endoscopy
And Other Interventional Techniques
Official Journal of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and European Association for Endoscopic Surgery (EAES)

ISSN 0930-2794
Volume 31
Number 11

Surg Endosc (2017) 31:4857-4862
DOI 10.1007/s00464-017-5698-3



Springer

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Risk factors for the late development of common bile duct stones after laparoscopic cholecystectomy

Yoo Shin Choi[1] · Jae Hyuk Do[2] · Suk Won Suh[1] · Seung Eun Lee[1] · Hyun Kang[3] · Hyun Jeong Park[4]

Received: 15 March 2017 / Accepted: 22 June 2017 / Published online: 29 June 2017

Abstract
Background The development of common bile duct (CBD) stones after laparoscopic cholecystectomy (LC) could be a stressful event for surgeons and patients. The purpose of this study was to investigate the risk factors for and the time of occurrence of CBD stones, which are detected at a certain period after LC in patients who have no history of having CBD stone before operation.
Methods A total of 1938 patients who underwent LC for benign gallbladder lesion were retrospectively analyzed. The patients were categorized into two groups according to the development of CBD stones at least 6 months after LC (case group, control group). The risk factors for and the time of development of CBD stones after LC were evaluated.
Results In a univariate analysis, the significant factors for the development of CBD stones were old age, acute cholecystitis, the presence of periampullary diverticulum, and the presence of gall bladder stones sized <0.55 cm. By multivariate analysis, acute cholecystitis (OR: 3.082, 95% CI: 1.306–7.272, $p = 0.010$), the presence of periampullary diverticulum (OR: 7.950, 95% CI: 3.425–18.457, $p < 0.001$), and the presence of gall bladder stones sized < 0.55 cm (OR: 5.647, 95% CI: 1.310–24.346, $p = 0.020$) were independent factors that could predict the development of CBD stones at least 6 months after LC. The time intervals of the development of CBD stones had evenly distributed during 50 months after LC.
Conclusion This study suggested that the surgeon should inform the possibility of the development of CBD stones who have the identified risk factors.

Keywords Common bile duct stone · Risk factor · Laparoscopy · Cholecystectomy

Common bile duct (CBD) stones are classified as primary and secondary based on the point of origin. In general, secondary CBD stones originate from the gallbladder (GB) and pass into CBD [1], and they form a large majority [1]. Laparoscopic cholecystectomy (LC) and operative CBD exploration or endoscopic retrograde cholangiopancreatography (ERCP) are mandatory therapeutic modalities in patients who have GB and CBD stone(s), to prevent complications related to the stone(s).

CBD stones are reported to occur in about 4.5–18% patients undergoing LC [2], and preoperatively undiagnosed CBD stones are found in 2.3–3.5% during LC [3, 4]. The development of CBD stones after LC could be a stressful event for surgeons and patients due to loss of quality of life, increased medical cost for treatment, the possibility of hospitalization. Although there have been reports on the risk factors and incidence of recurrence of CBD stone after endoscopic therapies/percutaneous bile drainage [5–10], and/or cholecystectomy following the removal of the initial CBD stones [11], previous studies

✉ Jae Hyuk Do
jhdo@cau.ac.kr

[1] Department of Surgery, College of Medicine, Chung-Ang University, Seoul, South Korea

[2] Department of Internal Medicine, College of Medicine, Chung-Ang University, 224-1 Heuksuk-dong, Dongjak-gu, 156-755 Seoul, South Korea

[3] Department of Anesthesiology and Pain Medicine, College of Medicine, Chung-Ang University, Seoul, South Korea

[4] Department of Radiology, College of Medicine, Chung-Ang University, Seoul, South Korea

included patients with already clearing CBD stones (history of prior CBD stone) before LC. Therefore, further studies on patients who have no evidence of CBD stones before LC (especially at a certain period after cholecystectomy) may be helpful to evaluate the risk factors and predict the interval of the development of CBD stones after LC. Moreover, we could select and identify patients who need to be closely followed up.

Herein, we investigated the risk factors for and the time of the development of CBD stones detected at a certain period after LC in patients who have no history of having CBD stones before operation.

Material and method

Patient selection and data collection

Between June 2008 and July 2015, 2104 patients underwent LC at Chung-Ang university hospital (Seoul, Korea). The aim of this study was to investigate the risk factor for occurrence of CBD stones in patients that had already received LC for benign disease. Thus, patients who had concomitancy or suspicion of CBD stones before LC, and biliary malignancy such as GB cancer, choledochal cyst, or cholangiocarcinoma were excluded. Also, patients with systemic diseases (hemolytic anemia, inflammatory bowel disease, etc.) [12] related to lithogenesis were excluded to avoid confusion with the aim of our study.

Finally, 1938 patients who received LC for benign GB lesion were retrospectively identified through a review of the GB database. All operations were performed by two surgeons who had experience of performing more than 500 LCs with a standard three- or four-port technique. A surgical closed drain was inserted according to the discretion of surgeons usually in case of complications of acute cholecystitis (hydrops, empyema, gangrene, pericholecystic abscess, etc.).

The following clinical data were collected from all patients at presentation: age, sex, body mass index (BMI), smoking, diabetes mellitus, history of a preoperative gastric surgery, and laboratory results. In addition, the cause of operation, severity in case of acute cholecystitis, size and number of GB stone(s), the presence of periampullary diverticulum, preoperative CBD diameter, distal CBD angulations, and the time of detection of CBD stones after LC were investigated. Acute cholecystitis was decided according to the Tokyo Guidelines [13]. The CBD diameter and distal CBD angulations were measured by one radiologist on computed tomography (CT), magnetic resonance imaging (MRI), or cholangiogram, which was performed before LC [8].

Of 1938 patients who received LC for benign GB lesion, patients who developed CBD stones at least 6 months after LC were categorized as the CASE group and the remaining were the CONTROL group.

The time of detection of CBD stone after LC was determined when a patient visited the hospital for obstructive jaundice (elevation of the serum liver enzymes/bilirubin) or right upper area pain, and the presence of CBD stones was confirmed on a radiological image such as an ultrasound, CT, MRI, or ERCP. The time of development of CBD stones was calculated from LC to detection of CBD stone, and in the case of the CONTROL group, we regarded that there were no CBD stones until the date of study.

This cohort study used a questionnaire and was approved by the Institutional Review Board of Chung-Ang University Hospital.

Statistical analysis

For continuous variables, the distribution of the data was first evaluated for normality using the Kolmogorov–Smirnov test. As all variables did not pass the normality test, we additionally checked the Q–Q plots, which did not indicate a significant deviation from linearity. Thus, we allowed the normal assumption for a parametric test, and the groups were compared using Student's *t*-tests. Descriptive variables were subjected to $\chi 2$ analysis or Fisher's exact test, as appropriate.

To identify the significant risk factors for the development of CBD stone after LC, multiple logistic regression with backward selection was used. The optimal cut-off value for the size of GB stones was determined by the area under the receiver operating characteristic analysis. The identified cut-off value was 0.55 cm, and area under curve was 0.644 ($p = 0.015$).

The multicollinearity diagnostic indicated no multicollinearity issues (condition indices < 30; VIF values < 10) between the chosen independent variables in this study. Factors that had univariate p values of < 0.1 were included for multivariate analysis.

Data are presented as median (P_{25}–P_{75}), odds ratio (OR) (95% confidence interval (CI)), or absolute number (%). p value of < 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS 23.0 (IBM Corp., Armonk, NY, USA).

Result

Patient characteristics

The mean age of the entire cohort was 52.0 years (range, 6.0–91.0 years): 930 (48.0%) patients were men. The mean BMI was 24.5 kg/m^2 (range, 10.9–65.8 kg/m^2).

In the entire cohort, the CASE group included 26 (1.3%) patients and the CONTROL group included 1912 (98.7%) patients. The mean age was significantly higher in the CASE group (62.4, range: 30–87 years) than in the CONTROL group (51.2, range: 6–91 years) (Table 1).

Risk factors for the development of CBD stone after LC

In the univariate analysis, old age, ($p = 0.001$), acute cholecystitis ($p < 0.001$), the presence of periampullary diverticulum ($p < 0.001$), and the presence of GB stones <0.55 cm ($p < 0.001$) were found to be risk factors (Table 1). In the multivariate analysis, acute cholecystitis (OR 3.082, 95% CI, 1.306–7.272, $p = 0.010$), the presence of periampullary diverticulum (OR 7.950, 95% CI, 3.425–18.457, $p < 0.001$), and the presence of GB stones <0.55 cm (OR 5.647, 95% CI, 1.310–24.346, $p = 0.020$) were all independent factors that could predict the development of CBD stones at least 6 months after LC (Table 2).

The time of detection of CBD stone after LC

CBD stones developed from 6.1 to 52.7 months after LC (median time was 16.3 months) and were evenly distributed during the whole follow-up period (Figure 1).

Discussion

The incidence of clinically significant developed CBD stone at least 6 months after LC was 1.34% (26/1938 patients) in our study. This finding is similar to the result from a previous study [14].

There is no clear definition for referring CBD stone after LC. According to a previous study, the development of CBD stone was considered in cases of recurrent stones, which were found at least 6 months after ERCP; therefore, we also defined the development of CBD stone as the development of CBD stones at least 6 months after LC in patients [15–17]. Although the above-mentioned criterion could not be adjusted to the development of CBD stone after LC, at least the CBD stones that were concomitant during LC or passed into the CBD during LC would be excluded.

Periampullary diverticulum is one of the well-known factors implicated in primary and recurrent CBD stones caused by the compression of the periampullary diverticulum at the end of the CBD and the dilatation of CBD by periampullary diverticulum [18–24]. Previous studies revealed that cholecystectomy in patients with periampullary diverticulum does not prevent the development of recurrent CBD stones, and periampullary diverticulum predisposes patients to primary rather than secondary CBD

Table 1 Patient characteristics

	Case group $N = 26$	Control group $N = 1912$	p value
Age (years)	65.0 (55.0–72.3)	52.0 (38.0–63.0)	<0.001
Sex M:F (*n*)	17:9	930:1008	0.074
BMI (kg/m^2)	23.7 (20.9–25.5)	24.5 (22.2–27.0)	0.136
Smoking: *n* (%)	2 (7.7)	427 (22.0)	0.076
DM: *n* (%)	6 (23.1)	231 (11.9)	0.077
Preoperative gastric surgery: *n* (%)	1 (3.8)	50 (11.9)	0.682
Total bilirubin (mg/dL)	0.85 (0.60–1.30)	0.70 (0.50–1.10)	0.314
AST (IU/L)	23.0 (17.8–46.3)	26.0 (20.0–40.0)	0.213
ALT (IU/L)	20.5 (14.0–37.0)	26.0 (16.0–56.0)	0.186
ALP (IU/L)	171.5 (79.5–276.8)	208.0 (153.0–286.0)	0.318
Amylase (IU/L)	58.0 (31.0–77.5)	49.0 (38.0–66.0)	0.635
Chronic hepatitis B	1 (3.8)	91 (4.7)	0.650
Acute cholecystitis: *n* (%)	17 (65.4)	580 (29.9)	<0.001
Periampullary diverticulum: *n* (%)	13 (50.0)	234 (12.1)	<0.001
Presence of GB stone < 0.55 cm	22 (84.6)	1136 (59.4)	0.009
Multiple GB stone	408/1360	410/1382	0.983
Preoperative CBD diameter (mm)	8.2 (5.8–9.1)	6.1 (4.7–7.9)	0.012
Preoperative CBD angulations (°)	134.0 (125.5–145.9)	136.4 (126.2–144.5)	0.743

Data are presented as median (P_{25}–P_{75}) or absolute number (%)

CASE group, patients who have developed CBD stone at least 6 months after LC; CONTROL group, patients who have not developed CBD stone after LC

BMI Body mass index; *DM* diabetes mellitus; *AST* aspartate transaminase; *ALT* alanine transaminase; *ALP* alkaline phosphatase; *GB* gallbladder; *CBD* common bile duct; *LC* laparoscopic cholecystectomy

Table 2 Univariate and Multivariate Analyses of the Risk factors for the late development of CBD stones after LC

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age (years)	1.048	1.020–1.076	0.001			
Sex	0.484	0.215–1.091	0.080			
BMI (kg/m^2)	0.906	0.808–1.016	0.090			
Smoking	0.292	0.069–1.239	0.095			
DM	2.249	0.894–5.660	0.085			
Preoperative gastric surgery	1.521	0.202–11.451	0.684			
Total bilirubin (mg/dL)	1.026	0.866–1.215	0.767			
AST (IU/L)	0.996	0.987–1.005	0.419			
ALT (IU/L)	0.995	0.986–1.003	0.220			
ALP (IU/L)	0.999	0.997–1.002	0.509			
Amylase (IU/L)	1.000	0.997–1.002	0.811			
Chronic hepatitis B	0.000	0.000	0.997			
Acute cholecystitis	4.509	1.998–10.176	<0.001	3.082	1.306–7.272	0.010
Periampullary diverticulum	7.308	3.345–15.966	<0.001	7.950	3.425–18.457	<0.001
Presence of GB stone < 0.55 cm	3.757	1.290–10.945	0.015	5.647	1.310–24.346	0.020
Multiple GB stone	3.300	0.773–14.093	0.107			
Preoperative CBD diameter	1.009	0.975–1.045	0.600			
Preoperative CBD angulations	0.996	0.970–1.023	0.775			

BMI body mass index; *DM* diabetes mellitus; *AST* aspartate transaminase; *ALT* alanine transaminase; *ALP* alkaline phosphatase; *GB* gallbladder; *CBD* common bile duct; *LC* laparoscopic cholecystectomy

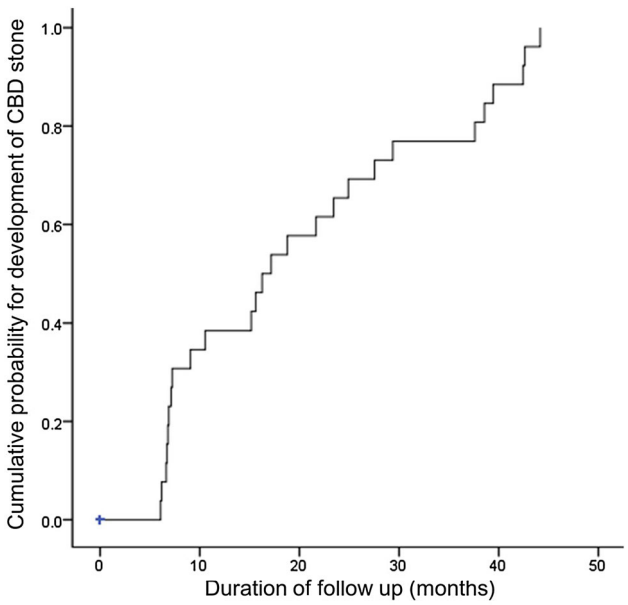

Fig. 1 The cumulative rate for the development of CBD stone. The time interval of the development of CBD stone is evenly distributed during the follow-up period

stones [18, 22]. The results of our study are also in accordance with these observations.

Indeed, bile stasis is thought to be an important factor in the pathogenesis of CBD stones [25, 26]. Angulation along the course of the CBD may predispose to bile stasis, and thus, promote stone formation and recurrence [8]. A previous report had suggested that the mean angulation of CBD was 103.4° in patients with concurrent choledocholithiasis as compared with 135.7° in patients with cholecystolithiasis only, and duct dilation (≥13 mm) may promote stasis, thereby supporting the notion of its pathogenetic importance [8]. In our study, the median angulation of CBD was 134° in the CASE group (136° in the CONTROL group), and the median CBD diameter was 8.2 mm in the CASE group (6.1 mm in the CONTROL group) with no significant differences between the two groups by multivariate analysis.

Our study revealed that the development of CBD stone commonly occurred after LC due to acute cholecystitis [12]. LC for acute cholecystitis is generally more difficult and the operation time is generally longer than chronic cholecystitis or other symptomatic GB disease. As the operation time becomes more protracted, the probability of GB stone transmission to the CBD through the cystic duct will rise [27]. The incidence of retained CBD stone is significantly higher in those requiring open cholecystectomy and is a reflection of their more complex disease [28, 29].

A cystic duct dilatation in the GB stone population is directly associated with the passage of GB stones into the bile ducts to form a secondary bile duct stone, and the narrow caliber and spiral valve of the cystic duct would

make for more favorable transmission of smaller stones [1, 27]. In other words, the smaller size of GB stones would enable them easily pass into the cystic duct than a large-sized stone, and our study revealed that a small GB stone, especially less than 0.55 cm, is the one of the risk factors for the development of CBD stone after LC.

Cox et al. [30] reported that the median time for presentation of retained CBD stones after LC is 4 years (range: 6 days–18 years) and the distribution was skewed with a quarter presenting in the first 12 months, half by 4 years. However, in our study, the median time for the development of CBD stone after LC was 16.3 months, and in 38.5% (10/26) patients, it was presented within 1 year. Since then, CBD stones consistently developed during the follow-up period. Similar to a previous study [30], as the data of this study were retrospectively collected and included according to the clinical presentation, the percentage of patients with small, retained CBD stones that pass spontaneously is unknown. Currently, there is no mechanism for predicting which stones may pass and which shall cause serious clinical problem. This study has a limitation in that it is a retrospective analysis. Hence a prospective study with a long-term follow-up period would be necessary.

In conclusion, this study suggested that acute cholecystitis, periampullary diverticulum, and the presence of GB stones sized <0.55 cm could be independent risk factors for the development of CBD stones at least 6 months after LC and detected consistently. Therefore, the surgeon should inform the possibility of the development of CBD stones after LC to the patients who have these risk factors even for long term after the operation.

Acknowledgments None.

Compliance with ethical standards

Disclosures Yoo Shin Choi, Jae Hyuk Do, Suk Won Suh, Seung Eun Lee, Hyun Kang, and Hyun Jeong Park have no conflicts of interest or financial ties to disclose.

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