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ORIGINAL ARTICLE

Prevalence and Predictors of Unnecessary Endoscopic Retrograde Cholangiopancreatography in the Two-Stage Endoscopic Stone Extraction Followed by Laparoscopic Cholecystectomy

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Abstract

Backgrounds A two-stage procedure involving endoscopic retrograde cholangiopancreatography (ERCP), followed by cholecystectomy, is one of the primary treatments of concomitant gallstones and choledocholithiasis. However, negative findings on ERCP and migrating gallstones after cholecystectomy are major concerns. This study aimed to identify the prevalence of unnecessary ERCP and to develop and validate a predictive nomogram using preoperative factors in patients who underwent a two-stage procedure.

Methods Consecutive 931 patients were treated with the two-stage procedure for evident gallstones and suspected choledocholithiasis. After the cholecystectomy, a cholangiogram was performed to confirm the absence of the migrating gallstones. The patients were divided into derivation ($n = 652$) and validation ($n = 279$) cohorts.

Results A total of 26.5% (247/931) patients had unnecessary ERCP (negative choledocholithiasis, 14.6%; migrating gallstones, 11.9%). No stones on images ($P < 0.001$), total bilirubin < 1.2 mg/dL ($P = 0.006$), and common bile duct diameter < 8.0 mm ($P = 0.004$) were independent factors associated with negative finding on ERCP with a validated nomogram area under the curve (AUC) of 0.72 (95% confidence interval [CI] 0.64–0.80). For migrating gallstones after cholecystectomy, radiolucent gallstones ($P < 0.001$), gallstone size ≤ 6.4 mm ($P = 0.001$), cystic duct stones ($P < 0.001$), gallbladder wall thickness ≥ 3.2 mm ($P = 0.003$), and low-lying cystic duct ($P < 0.001$) were independent factors with a validated nomogram AUC of 0.77 (95% CI 0.68–0.87).

Conclusions About one fourth of the patients may have unnecessary ERCP in the two-stage procedure. Based on our nomogram using preoperative factors, high-risk patients who are more likely to perform unnecessary ERCP could be considered for the one-stage procedure.

Keywords Endoscopic retrograde cholangiopancreatography · Cholecystectomy · Gallstones · Choledocholithiasis · Two-stage procedure

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Introduction

About 10–15% of patients with gallstones present concomitant choledocholithiasis.[1–3] Laparoscopic cholecystectomy (LC) is now widely accepted as the first choice for the treatment of symptomatic gallstones. However, when gallstones and choledocholithiasis are concomitant, their management is controversial for both surgeons and endoscopists.[4, 5]

Until today, the confirmed or suspected cases of choledocholithiasis have been routinely managed by the two-stage procedure using preoperative endoscopic retrograde cholangiopancreatography (ERCP) and then followed by LC.[6, 7] With the advancement of endoscopic and laparoscopic

surgical techniques, several alternative approaches, such as laparoscopic common bile duct (CBD) exploration (LCBDE) or intraoperative ERCP, have been gradually developed to treat concomitant gallstones and choledocholithiasis.[8, 9]

Although the two-stage procedure using ERCP has been proven to be a safe and effective treatment in most cases, this may cause a substantial number of unnecessary preoperative drainage even in those patients with strict criteria. Moreover, gallstones can sometimes move to the CBD because of a spontaneous migration or manipulation during cholecystectomy, leading to an additional endoscopic procedure and longer hospital stay.[10] To prevent these unnecessary procedures, a method of accurately predicting choledocholithiasis and migrating gallstones in the preoperative setting is very important.

The aim of this study was to evaluate the prevalence and predictors of unnecessary ERCP associated with the two-stage procedure, and then to create a feasible patient-based nomogram to identify preoperative predictors. The hypotheses were that the one-stage procedure had a practical application limitation due to equipment requirements, technical skills, and prolonged operation time. Therefore, knowing the preoperative risk factors associated with unnecessary ERCP in the two-stage procedure can lead to the performance of a single-stage procedure.

Material and Methods

Study Design and Population

This retrospective study was conducted between January 2015 and February 2017 at a single tertiary medical center. Patients who underwent initial ERCP followed by cholecystectomy due to gallstones and suspected or evident choledocholithiasis were included in the study. During the study period, the one-stage procedure with cholecystectomy and intraoperative cholangiogram (IOC) with or without ERCP was not available. The final data set was divided into the following groups: the derivation cohort for the development of a predictive model (conducted from January 2015 to August 2016) and the validation cohort for the validation of the predictive model (conducted until February 2017).

Patients with evident gallstones and choledocholithiasis underwent biochemical laboratory test and imaging studies (ultrasound [US], endoscopic US [EUS], computed tomography [CT], and magnetic resonance cholangiopancreatography [MRCP]). We included patients with clinical suspicion of choledocholithiasis (biliary colic), with elevated levels of liver function test, or suspicion of gallstone pancreatitis, and dilated CBD or suspicion of choledocholithiasis on imaging, done currently or in the previous 6 months. Dilated CBD was defined as when the maximal diameter of the CBD exceeded 7 mm in patients with gallbladder in situ.[11] Patients were excluded if they had (i) undergone prior cholecystectomy, (ii) not undergone ERCP because of the absence of choledocholithiasis on the cholangiogram after percutaneous transhepatic gallbladder (GB)/bile duct drainage (PTGBD/PTBD), and (iii) other procedures, such as percutaneous transhepatic cholangiography to remove choledocholithiasis. Among the patients who underwent ERCP, (iv) cholecystectomy was not performed due to comorbidity, old age, and their refusal to the procedure. (v) Patients who have undergone another procedure during ERCP (endoscopic transpapillary gallbladder drainage, or endoscopic ultrasound-guided GB drainage) and (vi) patients with removed or dislodged endoscopic nasobiliary drainage (ENBD) tube before and after the operation were excluded in this study. Prospectively collected database related to the inclusion criteria, demographics, clinical characteristics, laboratory results, and imaging results were retrospectively reviewed. We also analyzed the outcomes not only of the ERCP but also of the cholecystectomy operation including the length of hospital stay.

This study was approved by the institutional review board of our hospital (IRB number: 2016-1079) and written informed consent was obtained from all patients.

Study Protocol

Procedures were identical in the derivation and validation cohorts of this study. The diagnostic work up of all patients included a biochemical test of the liver function and abdominal CT as a primary imaging modality. If suspected gallstones are invisible on the CT scan, US or EUS was performed as an ancillary imaging modality. The positive US or EUS finding was defined as the presence of a hyperechoic lesion with/without posterior acoustic shadowing in the gallbladder, including sludge such as non-shadowing echo layering. A diagnosis of choledocholithiasis on CT was made when there was direct visualization of a stone or particle in the CBD described by experienced radiologists. Patients with a high probability of choledocholithiasis with an elevated liver function test without visible choledocholithiasis on the CT scan underwent MRCP and/or EUS. Radiolucent gallstones are gallstones not detected by CT scan but show up on US/EUS or MRCP. Gallstone size is the largest stone measured. GB wall thickness is the thickest part of the GB on the imaging modalities. When cystic duct joins the CBD at its lower third as seen on the CT coronal view and/or MRCP, it was defined as a low-lying cystic duct. The maximal CBD diameter is the widest part of the CBD on the CT scan.

ERCP was performed by six endoscopists who are experts in the use of ERCP. A choledocholithiasis on ERCP was defined as definite filling defect on cholangiogram and confirmed based on visual assessment of endoscopy within the duodenum. If there is only sludge or sand-like bile without choledocholithiasis detected on the ERCP, we considered it as choledocholithiasis because sludge can cause cholangitis and pancreatitis.[12] A balloon occlusion-completion cholangiography was performed to

confirm the absence of stones in the CBD. After confirming that there is no remaining choledocholithiasis, all patients had routine ENBD (5 Fr in diameter, Cook Medical, Bloomington, IN) at the end of the procedure to confirm retained CBD stones or immediate migrating gallstones. The advantages of the placement of ENBD tube in two-stage procedure may be the following; first, cholangiogram via ENBD for the identification of CBD clearance after immediate ERCP may minimize the risk of "retaining CBD stones" before cholecystectomy. Second, the utility of ENBD in two-stage procedure may be attractive because simple removal of ENBD tube or additional ERCP could be determined according to the presence of "migrating CBD stones" on tubogram via ENBD tube following cholecystectomy. After the insertion of the ENBD tube, a second cholangiogram via the ENBD tube was performed to confirm the absence of the choledocholithiasis. On the next day after the cholecystectomy, we routinely performed cholangiogram via ENBD tube in patients to identify the presence of immediate migrating gallstones. Based on ERCP and pathology finding, the stones were classified into black, brown, pure cholesterol, and mixed stones based on color and shape in ERCP and pathologic finding.[13, 14] The flow protocol of this study is shown in Suppl. Fig. 1.

In this study, unnecessary ERCP prior to cholecystectomy was defined as the performance of initial ERCP followed by cholecystectomy in patients with concomitant gallstones and choledocholithiasis at hospitalization despite being negative for choledocholithiasis on ERCP and/or the presence of immediate migrating gallstones after cholecystectomy, requiring second attempt of ERCP during hospitalization.

Statistical Analysis

Continuous variables are presented as means (± standard deviation [SD]), which were compared using a Student's *t* test. Categorical variables were described as frequencies and percentages, which were compared using the chi-squared test or Fisher's exact test. Variables with a significant association on the univariate analysis (P value < 0.2) were entered into a stepwise logistic regression. The results of the multivariate logistic regression analyses are expressed as odds ratios (OR) and 95% confidence interval (CI). A predictive scale was built considering the variables that proved to be statistically significant in the multivariate analysis. Based on the relative weights of the significant predictors, a nomogram was produced to make patient-specific predictions. The area under the receiver operating characteristic (ROC) curve (AUC) was used to calculate the optimum cut-off to predict optimal sensitivity and specificity and to assess the discriminative ability of the nomogram. A P value $< .05$ indicates statistically significant differences. The statistical analysis was performed using SPSS version 21.0 (Armonk, New York, USA).

Result

Patient Population

Between January 2015 and February 2017, of the 1398 patients with suspected or evident choledocholithiasis besides their gallstones, 467 patients were excluded and 931 patients were finally assigned to a two-step treatment combining ERCP and cholecystectomy for the management of concomitant gallstones and choledocholithiasis. The first 652 patients were included in the derivation cohort and the remaining 279 patients comprised the validation cohort (Fig. 1).

Table 1 compares patient demographics, clinical characteristics, laboratory, and imaging data during the admission of the two cohorts. The mean age of both cohorts was 57.8 (± 15.4) years, and 52.2% of the subjects were male. Over half of the patients ($n = 515$, 55.3%) had some comorbidities. Sixty-four (6.9%) and 77 (8.3%) patients had a previous history of ERCP for choledocholithiasis and of abdominal surgery, respectively. The leading cause of patient admission was abdominal pain (81.3%), including 162 (17.4%) patients diagnosed with acute pancreatitis. Nearly all patients underwent CT (99.0%), followed by US (31.5%), MRCP (30.0%), and EUS (20.9%). No significant differences were present in the baseline characteristics between the two consecutive cohorts.

Prevalence of Choledocholithiasis on ERCP According to the American Society for Gastrointestinal Endoscopy Guideline Classification

In the 931 patients, 775 (83.2%), 154 (16.5%), and 2 (0.2%) patients met the ASGE criteria of the high-risk, intermediate-risk, and low-risk groups, respectively.

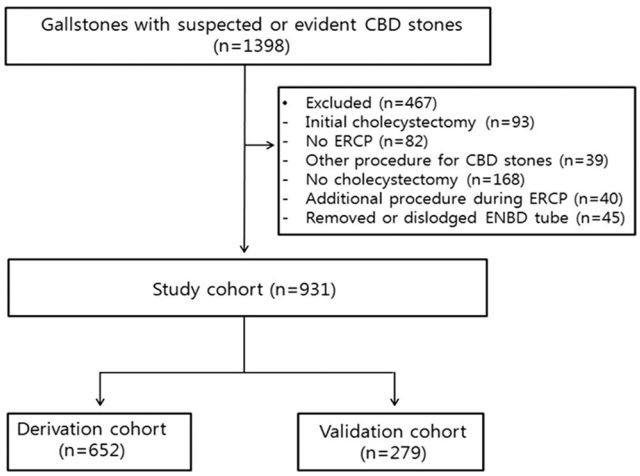

Fig. 1 Patient's flow diagram. CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; ENBD, endoscopic nasobiliary drainage

Table 1 Baseline characteristics in the derivation cohort and validation cohort

Variable	Total ($N = 931$)	Derivation cohort ($N = 652$)	Validation cohort ($N = 279$)	P value
Demographic factors				
Age (year)	57.8 ± 15.4	57.6 ± 15.3	58.4 ± 15.6	0.393
Male	486 (52.2%)	343 (52.6%)	143 (51.3%)	0.759
BMI (kg/m^2)	24.5 ± 3.5	24.5 ± 3.5	24.5 ± 3.4	0.926
Smoking	228 (24.5%)	152 (23.3%)	76 (27.2%)	0.233
Alcohol-drinking	410 (44.0%)	290 (44.5%)	120 (43.0%)	0.733
Clinical factors				
ASA classification				0.282
I	416 (44.7%)	280 (42.9%)	136 (48.7%)	
II	395 (42.4%)	288 (44.2%)	107 (38.4%)	
III	116 (12.5%)	82 (12.6%)	34 (12.2%)	
IV	4 (0.4%)	2 (0.3%)	2 (0.7%)	
History of ERCP	64 (6.9%)	44 (6.7%)	20 (7.2%)	0.928
Previous abdominal surgery	77 (8.3%)	57 (8.7%)	20 (7.2%)	0.504
Symptoms at admission[a]				
Abdominal pain	757 (81.3%)	530 (81.3%)	227 (81.4%)	> 0.999
Pancreatitis	162 (17.4%)	113 (17.3%)	49 (17.6%)	> 0.999
Fever	48 (5.2%)	32 (4.9%)	16 (5.7%)	0.718
Jaundice	94 (10.1%)	64 (9.8%)	30 (10.8%)	0.752
Laboratory characteristics				
WBC (10^3/μL)	9.1 ± 4.0	9.0 ± 4.0	9.3 ± 3.9	0.153
AST (IU/L)	215.8 ± 335.5	210.9 ± 308.3	227.0 ± 392.2	0.862
ALT (IU/L)	220.3 ± 253.4	214.6 ± 241.7	233.5 ± 278.9	0.556
ALP (IU/L)	163.1 ± 128.8	163.4 ± 131.0	162.4 ± 123.9	0.917
r-GT (IU/L)	329.9 ± 311.6	326.2 ± 299.2	338.3 ± 339.0	0.823
Total bilirubin (mg/dL)	2.6 ± 3.1	2.6 ± 3.3	2.5 ± 2.6	0.649
Amylase (U/L)	252.1 ± 669.0	241.4 ± 583.8	276.9 ± 835.7	0.769
Lipase (IU/L)	618.8 ± 2076.5	636.0 ± 2142.9	578.7 ± 1915.6	0.624
Imaging modalities				0.562
CT	922 (99.0%)	645 (98.9%)	277 (99.3%)	
EUS	195 (20.9%)	144 (22.1%)	51 (18.3%)	
MRCP	280 (30.0%)	200 (30.7%)	80 (28.7%)	
US	293 (31.5%)	215 (33.0%)	78 (28.0%)	

[a] Overchecking-symptoms available

Data in table are presented as the mean ± standard deviation (SD) or as the number (of patients) with percentage

BMI, body mass index; *ASA*, American society of anesthesiologists; *ERCP*, endoscopic retrograde cholangiopancreatography; *WBC*, white blood cell; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase; *ALP*, alkaline phosphatase; *r-GT*, gamma-glutamyl transferase; *CT*, computed tomography; *EUS*, endoscopic ultrasound; *MRI*, magnetic resonance imaging; *US*, ultrasound

Among them, 89.0% (690/775) of the patients in the high-risk and 68.1% (105/154) patients in the intermediate-risk were found to have choledocholithiasis on ERCP ($P < 0.001$). None of the patients in the low-risk group had choledocholithiasis. The overall incidence of choledocholithiasis on ERCP was 85.4% (795/931), and 14.6% (136/931) of the patients showed negative choledocholithiasis on ERCP in our study cohort (Suppl. Table 1).

Prevalence of Immediate Migrating Gallstones After the Two-Stage Procedure

In our study, the overall incidence of the presence of immediate migrating gallstones in patients who underwent initial ERCP followed by cholecystectomy was 11.9% (111/931). No significant difference was found between the derivation and validation cohorts (11.9 vs. 11.8%, $P = 0.953$).

Prevalence of Unnecessary ERCP in the Two-Stage Procedure

Unnecessary ERCP was performed in 26.5% (negative choledocholithiasis on ERCP, 14.6%; immediate migrating gallstones, 11.9%) of the patients with concomitant gallstones and choledocholithiasis in the two-stage procedure with ERCP followed by cholecystectomy.

Diagnostic Value of EUS in Patients with Choledocholithiasis but a Negative CT Scan

EUS was performed in 88 patients out of 249 patients with negative CT findings of choledocholithiasis. Among these 88 patients, EUS revealed choledocholithiasis in 77 (87.5%) patients, and 71 (80.7%) patients were confirmed to have choledocholithiasis by ERCP. Six (6.8%) patients were ultimately found not to have choledocholithiasis using ERCP, despite positive EUS finding. Among 11 (12.5%) patients with negative EUS findings, 3 (3.4%) patients were confirmed to have choledocholithiasis, but 8 (9.1%) patients were not demonstrated by ERCP. The diagnostic accuracy of EUS for choledocholithiasis but a negative CT scan was 90.3% (95% CI 0.82–0.95) with sensitivity of 92.4% (95% CI 0.88–0.95), specificity 73.0% (95% CI 0.43–0.92), positive predictive value of 96.7% (95% CI 0.92–0.99), and negative predictive value of 57.8% (95% CI 0.34–0.72). The rate of unnecessary ERCP in the EUS group was 13.2%, compared with 14.4% in the group without EUS; there was no significant difference between the two groups (P =0 .721).

Predictive Factors of Negative Choledocholithiasis on ERCP in the Derivation Cohort

In the derivation cohort with 652 patients, the baseline characteristics did not show any significant difference between the groups with and without choledocholithiasis except for the history of ERCP, total bilirubin level, presence of choledocholithiasis on imaging, and maximal CBD diameter (Table 2). In the univariate analysis, the predictive factors associated with negative choledocholithiasis on ERCP were absence of ERCP history, total bilirubin level, absence of choledocholithiasis, and maximal CBD diameter on imaging. Total bilirubin of < 1.2 mg/dL and maximal CBD diameter of < 8.0 mm were considered as cut-off points using ROC. The multivariate model yielded 3 factors that were independently and significantly associated with the absence of choledocholithiasis. Total bilirubin of < 1.2 mg/dL (OR 1.95, 95% CI 1.22–3.15; P = 0.006), absence of choledocholithiasis on imaging (OR 5.19, 95% CI 3.21–8.57; P < 0.001), and maximal CBD diameter of < 8.0 mm (OR 2.05, 95% CI 1.26–3.39; P = 0.004). These developed parameters had a good performance in the prediction of negative choledocholithiasis: AUC 0.76 (95% CI 0.71–0.81) with a sensitivity of 63.0% (95% CI 52.3–72.9), a specificity of 78.4% (95% CI 74.7–81.7), and an accuracy of 76.2% (95% CI 72.7–79.4) (Table 3).

Predictive Factors of Immediate Migrating Gallstones with the Two-Stage Procedure in the Derivation Cohort

In the derivation cohort, there were no significant differences in the baseline characteristics between the groups with and without migrating gallstones (Suppl. Table 2). Additional imaging data according to migrating gallstones were shown in Table 4. In the univariate analysis, the predictive factors associated with migrating gallstones were radiolucent gallstones, maximal size of gallstones, presence of cystic duct stones, maximal thickness of GB wall, and the cystic duct at the distal part of CBD. Gallstones ≤ 6.4 mm and GB wall thickness ≥ 3.2 mm were used as cut-off points. The multivariate model yielded 5 factors that were independently and significantly associated with the presence of migrating gallstones with the following predictive factors: radiolucent gallstones (OR 3.39, 95% CI 1.86–6.14; P < 0.001), maximal size of gallstones ≤ 6.4 mm (OR 2.49, 95% CI 1.43–4.44; P = 0.001), presence of cystic duct stones (OR 3.95, 95% CI 1.95–7.81; P < 0.001), maximal thickness of GB wall ≥ 3.2 mm (OR 2.24, 95% CI 1.32–3.85; P = 0.003), and a low-lying cystic duct (OR 6.32, 95% CI 3.09–12.84; P < 0.001). These developed parameters had a good performance in predicting the presence of migrating gallstones: AUC of 0.79 (95% CI 0.73–0.84) with a sensitivity of 76.9% (95% CI 66.0–85.7), a specificity of 70.6% (95% CI 66.6–70.6), and an accuracy of 71.3% (95% CI 67.7–74.8) (Table 5).

Nomogram Development

From the multivariate analysis in the derivation cohort, a nomogram that integrated 3 significantly independent predictive factors in negative choledocholithiasis on ERCP and 5 significant independent predictive factors in migrating gallstones after the two-stage procedure was developed, respectively. Points are assigned for each variable by drawing a line upward from the corresponding variable to the point line. The sum of the points plotted on the total point line corresponds to the risk prediction. A nomogram used to calculate the scale and the probability is presented in Suppl. Fig. 2.

Predictive Value of the Proposed Nomogram in the Validation Cohort

In the validation cohort with 279 patients, the nomogram maintained a significant discriminative ability; AUC of 0.72 (95% CI 0.64–0.80) with a sensitivity of 72.7%

Table 2 Characteristics according to the retained choledocholithiasis on ERCP in the derivation cohort

Variable	Total (N = 652)	None (*N* = 92)	Retained choledocholithiasis (*N* = 560)	*P* value
Demographic factors				
Age (year)	57.6 ± 15.3	55.8 ± 15.3	57.9 ± 15.3	0.170
Male	345 (52.9%)	47 (51.1%)	296 (52.9%)	0.753
BMI (kg/m^2)	24.5 ± 3.5	24.8 ± 3.9	24.4 ± 3.5	0.378
Smoking	152 (23.3%)	17 (18.5%)	135 (24.1%)	0.237
Alcohol-drinking	290 (44.5%)	44 (47.8%)	246 (43.9%)	0.486
Clinical factors				
ASA classification				0.787
I	280 (42.9%)	36 (39.1%)	244 (43.6%)	
II	288 (44.2%)	43 (46.7%)	245 (43.8%)	
III	82 (12.6%)	13 (14.1%)	69 (12.3%)	
IV	82 (12.6%)	0 (0.0%)	2 (0.4%)	
History of ERCP	44 (6.7%)	1 (1.1%)	43 (7.6%)	0.020
Previous abdominal surgery	57 (8.7%)	7 (7.6%)	50 (8.9%)	0.678
Symptoms at admission[a]				
Abdominal pain	530 (81.3%)	75 (81.5%)	455 (81.2%)	0.951
Pancreatitis	113 (17.3%)	14 (15.2%)	99 (17.7%)	0.563
Fever	32 (4.9%)	2 (2.1%)	30 (5.3%)	0.190
Jaundice	64 (9.8%)	10 (10.8%)	54 (9.6%)	0.714
Laboratory characteristics				
WBC (10^3/μL)	8.9 ± 3.9	8.9 ± 3.6	8.9 ± 4.0	0.945
AST (IU/L)	210.6 ± 307.7	177.1 ± 197.2	216.0 ± 321.9	0.256
ALT (IU/L)	214.4 ± 241.3	180.8 ± 184.4	219.9 ± 249.1	0.147
ALP (IU/L)	163.4 ± 130.8	152.1 ± 147.0	165.2 ± 128.0	0.371
r-GT (IU/L)	325.7 ± 299.0	282.5 ± 268.8	332.9 ± 303.3	0.132
Total bilirubin (mg/dL)	2.6 ± 3.3	2.0 ± 2.0	2.7 ± 3.4	0.005
Amylase (U/L)	240.6 ± 582.6	183.4 ± 487.0	249.9 ± 596.6	0.304
Lipase (IU/L)	633.2 ± 2138.4	467.9 ± 1759.9	660.2 ± 2194.2	0.417
Imaging characteristics				
Choledocholithiasis on imaging	428 (65.6%)	28 (30.4%)	400 (71.4%)	< 0.001
Maximal CBD diameter (mm)	8.8 ± 3.3	7.7 ± 2.7	8.9 ± 3.4	< 0.001

[a] Overchecking-symptoms available

Data in table are presented as the mean ± standard deviation (SD) or as the number (of patients) with percentage

BMI, body mass index; *ASA*, American society of anesthesiologists; *ERCP*, endoscopic retrograde cholangiopancreatography; *WBC*, white blood cell; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase; *ALP*, alkaline phosphatase; *r-GT*, gamma-glutamyl transferase; *CRP*, C-reactive protein

(95% CI 57.2–85.0), a specificity of 60.9% (95% CI 54.2–67.1), and an accuracy of 62.7% (95% CI 56.8–68.4) in negative choledocholithiasis on ERCP. For migrating gallstones after the two-stage procedure, the nomogram showed also significant discriminative power: AUC of 0.77 (95% CI 0.68–0.87) with a sensitivity of 66.7% (95% CI 48.2–82.0), a specificity of 74.0% (95% CI 68.0–79.4), and an accuracy of 73.1% (95% CI 67.5–78.2) (Suppl. Table 3). Calibration curves plotted for the probability of negative choledocholithiasis and migrating gallstones showed an optimal correlation between the predicted and observed nomogram values (Fig. 2).

Additional ERCP and Operation Findings in the Derivation Cohort

Among the 652 patients, 346 patients had choledocholithiasis except sludge, with 171 (49.4%) having black stones, 98 (28.3%) having brown stones, 63 (18.2%) having pure cholesterol stones, and 14 (4.0%) having mixed stones. The pure cholesterol choledocholithiasis on ERCP was significantly higher in the group with migrating gallstones (68.2 vs. 10.6%, $P < 0.001$). No correlation between the choledocholithiasis and periampullary diverticulum (30.2 vs. 26.1%, $P = .426$), CBD angulation (150 ± 14 vs. 153 ± 12 degree,

Table 3 Diagnostic accuracy for negative choledocholithiasis on ERCP in the derivation cohort

Variable	Logistic regression		AUC (95% CI)	Diagnostic performance (95% CI)			
	OR (95% CI)	*P* value		Threshold [a]	Sensitivity	Specificity	Accuracy
Univariable							
No history of ERCP	7.57 (1.62–134.99)	0.047	0.53 (0.52–0.55)	–	98.9 (94.1–100)	7.7 (5.6–10.2)	20.6 (17.5–23.9)
T-bilirubin (mg/dL)	0.9 (0.8–0.99)	0.046	0.57 (0.51–0.64)	< 1.2	51.1 (40.4–61.7)	63 (58.9–67)	61.3 (57.5–65.1)
Negative choledocholithiasis on image	5.71 (3.57–9.36)	< 0.001	0.7 (0.65–0.76)	–	69.6 (59.1–78.7)	71.4 (67.5–75.1)	71.2 (67.5–74.6)
CBD dilatation (mm)	0.87 (0.8–0.94)	0.001	0.62 (0.56–0.68)	< 8.0	66.3 (55.7–75.8)	55.4 (51.1–59.5)	56.9 (53–60.7)
Multivariable							
T-bilirubin < 1.2 mg/dL	1.95 (1.22–3.15)	0.006	0.76 (0.71–0.81)	≥ 0.76	63.0 (52.3–72.9)	78.4 (74.7–81.7)	76.2 (72.7–79.4)
Negative choledocholithiasis on image	5.19 (3.21–8.57)	< 0.001					
CBD dilatation < 8.0 mm	2.05 (1.26–3.39)	0.004					

[a] Threshold was calculated by Youden's index

OR, odds ratio; *CI*, confidence interval; *AUC*, area under the curve; *ERCP*, endoscopic retrograde cholangiopancreatography; *CBD*, common bile duct

$P = 0.061$), and time interval between admission and ERCP procedure (1.4 ± 1.3 vs. 1.5 ± 1.2 days, $P = 0.052$) was present. The absence of the cystic duct filling was measured by cholangiogram on ERCP, which was significantly higher in the group with migrating gallstones (44.8 vs. 22.6%, $P < 0.001$).

In cholecystectomy, 613 (94.0%) patients underwent a laparoscopic procedure, but no difference is found between this group and the group with migrating gallstones. The operative and pathologic analysis of the 530 patients with gallstones except sludge indicated that 319 (60.2%) patients had black stones, 139 (26.2%) had pure cholesterol stones, 70 (13.2%) patients had brown stones, and 2 (0.3%) patients had mixed stones. Pure cholesterol gallstones were significantly higher in the group with migrating stones than in the group with pigmented stones (24.5 vs. 7.6%, $P < 0.001$). No correlation between an increased incidence of migrating gallstones and time interval between the ERCP and cholecystectomy (4.6 ± 3.7 vs. 4.7 ± 2.8 days, $P = 0.729$) and operation duration (66.8 ± 44.9 vs. 70.4 ± 27.7 min, $P = 0.503$) was present. The patients in the migrating gallstone group did not have a significantly longer length of hospital stay (9.4 ± 4.3 vs. 10.0 ± 4.3 days, $P = 0.503$).

Discussion

In our study, the overall prevalence of choledocholithiasis on ERCP was 85.4%. On the contrary, unnecessary ERCP was performed in 26.5% (negative choledocholithiasis on initial ERCP, 14.6%; migrating gallstones after cholecystectomy, 11.9%) of the patients with concomitant gallstones and choledocholithiasis in the two-stage procedure. This current study focuses on the prevalence of unnecessary ERCP and evaluates the predictive factors of unnecessary ERCP in the two-stage procedure. Moreover, we developed and validated a clinical prediction nomogram for negative choledocholithiasis and migrating gallstones with the two-stage procedure based on objective markers. To our knowledge, our clinical model is the first prediction nomogram that attempts to evaluate simultaneously the risk of negative choledocholithiasis and migrating gallstones in patients with concomitant choledocholithiasis and gallstones. The multivariate model yielded 3 factors that were independently and significantly associated with the absence of choledocholithiasis. (1) total bilirubin of < 1.2 mg/dL, (2) absence of choledocholithiasis on imaging, and (3) maximal CBD diameter of < 8.0 mm. These developed parameters had a good performance in the prediction of negative choledocholithiasis with an accuracy of 76.2%. Moreover, the multivariate model yielded 5 factors that were independently and significantly associated with the presence of migrating gallstones with the following predictive factors: (1) radiolucent gallstones, (2) maximal size of gallstones ≤ 6.4 mm, (3) presence of cystic duct stones, (4) maximal thickness of GB wall ≥ 3.2 mm, (5) a low-lying cystic duct. These developed parameters had a good performance in predicting the presence of migrating gallstones with an accuracy of 71.3%. In the validation cohort, the nomogram maintained a significant discriminative ability with an accuracy of 62.7% (95% CI 56.8–68.4) in negative choledocholithiasis on ERCP. For migrating gallstones after the two-stage procedure, the nomogram showed also significant discriminative power with an accuracy of 73.1% (95% CI 67.5–78.2).

To date, preoperative ERCP is a safe and effective option for removing choledocholithiasis in most cases. In the USA, analyzing nationwide trends in the management for choledocholithiasis showed that the rates of ERCP in combination with LC increased from 52.8% in 1998 to 85.7% in 2013 and a total of 96.9% (36,048/37207) patients were treated with

Table 4 Imaging characteristics according to migrating gallstones in the derivation cohort

Variable	Total (N = 652)	None (*N* = 574)	Migrating gallstones (*N* = 78)	*P* value
Stone type in GB (vs. sludge type)	546 (83.7%)	476 (82.9%)	70 (89.7%)	0.171
Radiolucent gallstones	103 (15.8%)	75 (13.1%)	28 (35.9%)	< 0.001
Multiple gallstones	411 (63.0%)	363 (63.2%)	48 (61.5%)	0.770
Maximal size of gallstones (mm)	7.9 ± 6.6	8.2 ± 6.8	5.7 ± 4.6	0.001
Presence of choledocholithiasis	428 (65.6%)	371 (64.6%)	57 (73.1%)	0.178
Presence of cystic duct stone	62 (9.5%)	44 (7.7%)	18 (23.1%)	< 0.001
Maximal GB wall thickness (mm)	3.2 ± 1.2	3.1 ± 1.2	3.6 ± 1.4	< 0.001
GB collapse	63 (9.7%)	55 (9.6%)	8 (10.3%)	> 0.999
GB distension	303 (46.5%)	260 (45.3%)	43 (55.1%)	0.130
Pericolic infiltration	105 (16.1%)	96 (16.7%)	9 (11.5%)	0.315
Connected location to cystic duct				< 0.001
Proximal CBD	451 (69.2%)	411 (71.6%)	40 (51.3%)	
Middle CBD	155 (23.8%)	137 (23.9%)	18 (23.1%)	
Distal CBD	46 (7.1%)	26 (4.5%)	20 (25.6%)	

Data in table are presented as the mean ± standard deviation (SD) or as the number (of patients) with percentage

GB, gallbladder; *CBD*, common bile duct

ERCP + LC.[7] However, a major concern regarding the two-stage preoperative ERCP is the risk of choledocholithiasis on post-operative cholangiogram.[15] Furthermore, it can lead to a false-negative result in the laboratory and imaging tests for choledocholithiasis.[16]

To accurately select and minimized adverse events of ERCP, ASGE guideline currently suggests risk-stratified approach based on clinical, laboratory, and imaging results.[17] However, ASGE high-risk criteria showed more than 50% probability of choledocholithiasis, recently large cohort study demonstrated that more than a third of the patients would receive diagnostic ERCP.[18] Moreover, in another recent study, the application of ASGE guideline led to unnecessary ERCP in nearly half of cases.[19–21] In our cohort, 89.0% and 68.1% of the patients in the high- and intermediate-risk according to ASGE guideline had choledocholithiasis. This higher prevalence of choledocholithiasis that we included sludge in the ranges of choledocholithiasis and performed multiple and definitive imaging modality (e.g., CT followed by EUS or MRCP), so the patients who do not need ERCP will be excluded. Likewise, our developed parameters for the prediction of negative choledocholithiasis had adequate AUC of 0.76; many patients who did not need to perform ERCP could be excluded, because they did not found the choledocholithiasis or dilated CBD on imaging.

Previous meta-analysis reported 89% to 94% sensitivity and 94% to 95% specificity of EUS for detecting choledocholithiasis by ERCP.[22–24] Because EUS was performed in only about 20% of patients, so it did not a predictor of unnecessary ERCP in our study. However, the diagnostic accuracy of EUS for choledocholithiasis but a negative CT scan was 90.3% (95% CI 0.82–0.95); therefore, EUS is an accurate tool for the detection of choledocholithiasis, and can prevent the unnecessary ERCP in patients with suspected choledocholithiasis but a negative CT scan, if it is available.

IOC, LCBDE, or intraoperative ERCP allow for a more selective approach for the removal of choledocholithiasis, and thus the avoidance of unnecessary preoperative ERCP. They have the advantage of combining two procedures into a single minimally invasive operation. The use of IOC can provide information about the presence of choledocholithiasis and show a surgical roadmap during cholecystectomy.[25] IOC during cholecystectomy found retained or newly passed choledocholithiasis that were not recognized in about 12% of patients performing preoperative ERCP.[26] Several recent trials comparing LCBDE with the two-stage procedure reported that their CBD clearance and morbidity rates in treating choledocholithiasis were similar (91.7 vs. 88.1%).[27–29] Moreover, they suggested that the single-stage procedure had the potential merit of a shorter hospital stay.[7, 9, 28] A randomized clinical trial showed that the one-stage procedure had a significantly shorter length of hospitalization (median 5 vs. 8 days, $P < 0.001$), with fewer CBD investigation, and similar morbidity and quality of life.[30] However, the one-stage procedure is still a relatively new technique and is not a widely practiced routine procedure.[7, 31] It is a complex radiologic–endoscopic–surgical technique that needs high-level technical skill and equipment requirement. Moreover, a disadvantage of this procedure is its prolonged operation time, as compared with the LC alone.[31, 32] Therefore, patients who have these risk factors based on the developed nomogram should opt for cholecystectomy with laparoscopic stone extraction or intraoperative ERCP in a one-stage procedure.

Table 5 Diagnostic accuracy for migrating gallstones after two-stage procedure in the derivation cohort

Variable	Logistic regression		AUC (95% CI)	Diagnostic performance (95% CI)			
	OR (95% CI)	*P* value		Threshold [a]	Sensitivity	Specificity	Accuracy
Univariable							
Radiolucent gallstones	3.73 (2.19–6.25)	< 0.001	0.61 (0.56–0.67)	–	35.9 (25.3–47.6)	86.9 (83.9–89.6)	80.8 (77.6–83.8)
Maximal size of gallstones	0.93 (0.89–0.97)	0.002	0.61 (0.56–0.67)	≤ 6.4	70.5 (59.1–80.3)	54.9 (50.7–59.0)	56.7 (52.8–60.6)
Presence of cystic duct stones	3.61 (1.93–6.57)	< 0.001	0.58 (0.53–0.63)	–	23.1 (14.3–34.0)	92.3 (89.8–94.4)	84.0 (81.0–86.8)
Maximal GB wall thickness (mm)	1.38 (1.16–1.64)	< 0.001	0.64 (0.58–0.71)	≥ 3.2	62.8 (51.1–73.5)	62.0 (57.9–66.0)	62.1 (58.3–65.9)
Low-lying cystic duct	7.27 (3.79–13.8)	< 0.001	0.61 (0.56–0.66)	–	25.6 (16.4–36.8)	95.5 (93.4–97.0)	87.1 (84.3–89.6)
Multivariable							
Radiolucent gallstones	3.39 (1.86–6.14)	< 0.001	0.79 (0.73–0.84)	≥ 0.11	76.9 (66.0–85.7)	70.6 (66.6–70.6)	71.3 (67.7–74.8)
Maximal size of gallstones ≤ 6.4 mm	2.49 (1.43–4.44)	0.001					
Presence of cystic duct stones	3.95 (1.95–7.81)	< 0.001					
Maximal GB wall thickness ≥ 3.2 mm	2.24 (1.32–3.85)	0.003					
Low-lying cystic duct	6.32 (3.09–12.84)	< 0.001					

[a] Threshold was calculated by Youden's index

OR, odds ratio; *CI*, confidence interval; *GB*, gallbladder; *CBD*, common bile duct

One of the major limitations of our study was that the data were obtained from a single tertiary center and data validation was conducted in the same hospital cohort; thus, no separate external validation was provided. Therefore, results of this study could not be generalized in other patients and their performance in other hospital settings is not known. In addition, the clinical predictions presented in this study were based on the imaging study and were not considered based on the endoscopic and surgical nature of the procedure. In a clinical trial, the choledocholithiasis and migrating gallstones can potentially be affected by multiple factors, such as surgeon skills and endoscopic equipment used. However, this risk for bias was minimized by ERCP finding and operating aspect in our result. Finally, our study only included patients who underwent ERCP for highly suspected choledocholithiasis, therefore did not provide natural course of retaining or migrating common bile duct stones in patients without suspected choledocholithiasis following cholecystectomy. Further studies of the natural course of choledocholithiasis after cholecystectomy in patients without suspected choledocholithiasis may be needed.

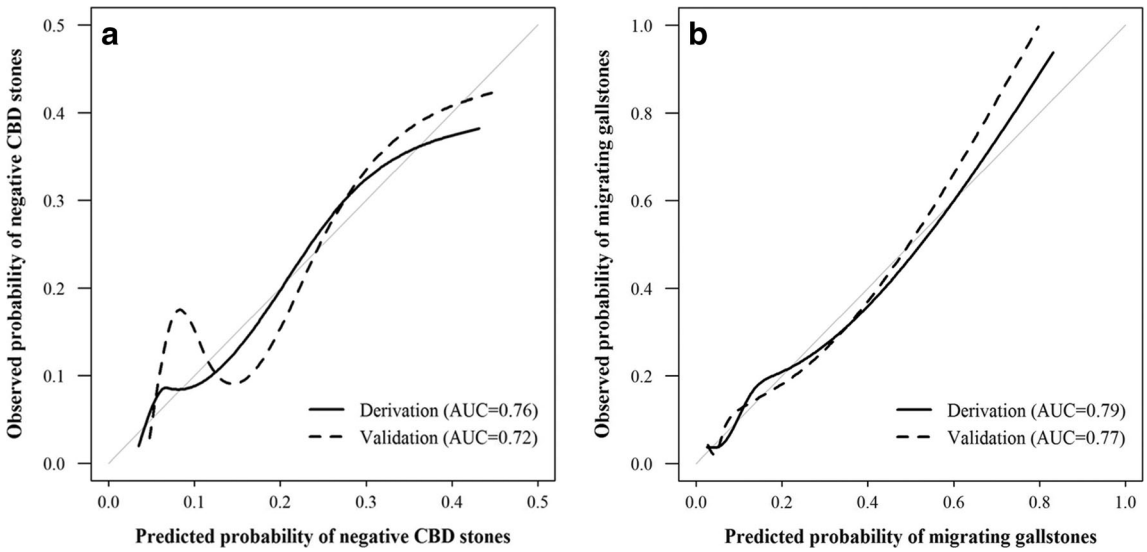

Fig. 2 Nomogram calibration plot of (**a**) negative choledocholithiasis on ERCP and (**b**) migrating gallstones after two-stage procedure. CBD, common bile duct

In summary, approximately one fourth of the patients in the two-stage procedure with ERCP followed by cholecystectomy may have undergone unnecessary ERCP prior to cholecystectomy and should have been candidates for the one-stage procedure. High-risk patients who might undergo unnecessary ERCP based on our nomogram using preoperative factors may be considered for the one-stage procedure when this surgical procedure and related resources are available.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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