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Risk factors for recurrence of common bile duct stones after endoscopic biliary sphincterotomy

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Abstract

Objective: Late complications after endoscopic biliary sphincterotomy (EST) include stone recurrence, but no definite risk factors for recurrence have been established. This study was performed to identify the predictors of recurrence and evaluate the clinical outcomes of EST for common bile duct stones.

Methods: In total, 345 eligible patients who successfully underwent EST were evaluated and followed up. Statistical analysis was performed on patients with recurrence or who had undergone at least 6 months of reliable follow-up to detect the risk factors for recurrence.

Results: A total of 57 patients (16.52%) developed recurrence of common bile duct stones. The median length of time until recurrence was 10.25 months (range, 6–54.4 months). Univariate analyses showed that the following factors were associated with recurrence: cholecystectomy prior to EST, prior biliary tract surgery, periampullary diverticulum, diameter of the common bile duct ($>$15 vs. $\leq$15 mm), quantity of stones, complete stone removal at the first session, and lithotripsy. Multivariate analysis identified two independent risk factors for recurrence: previous biliary tract surgery and lithotripsy.

Conclusions: EST for common bile duct stones is safe as indicated by patients' long-term outcomes. Patients with a history of biliary surgery or lithotripsy are more prone to recurrence.

Keywords

Common bile duct stones, endoscopic sphincterotomy, recurrence, risk factors, biliary surgery, lithotripsy

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Introduction

Endoscopic biliary sphincterotomy (EST) has been a widely accepted therapy for common bile duct stones (CBDS) since its introduction in 1974,[1] although this procedure is still associated with some challenges such as CBDS recurrence. Young patients may need more than one EST session to clear the ducts, and older or frail patients may develop severe and life-threatening adverse events because of recurrent stones and cholangitis. If predictors of recurrence could be detected in a timely manner, followed up closely, and treated early, the incidence of stone recurrence could theoretically be decreased, thus preventing biliary sepsis, biliary cirrhosis, or even death. Additionally, if follow-up evaluations could be restricted to high-risk patient populations, the cost of subsequent examinations may be reduced.

This study was performed to identify predictors of CBDS recurrence after EST and clarify the clinical course after EST.

Methods

Patients

We retrospectively analyzed patients with CBDS in the Affiliated Hospital of Inner Mongolia Medical University (Huhhot, China) from December 2013 to November 2015, where the average volume of endoscopic retrograde cholangiopancreatography (ERCP) was 650 to 800 procedures per year during the last 8 years. Patients referred from other hospitals and outpatients were excluded from the study because their clinical course during and after the procedure could not be easily assessed according to the same standard. Patients with biliary malignancy, hemolytic anemia, severe liver disease (liver cirrhosis or hepatocellular carcinoma), and abdominal surgery involving the liver or pancreas were also excluded. The diagnosis of CBDS was based on radiological visualization (ultrasonography, computed tomography, magnetic resonance cholangiopancreatography, and T-tube cholangiography) of CBDS and/or the presence of cholestasis (high levels of γ-glutamyl transferase, alkaline phosphatase, and total bilirubin). This study was approved by the ethics committee of our hospitals. All patients provided written informed consent before the operation. Finally, 345 inpatients who successfully underwent EST at our institutions and were followed up for more than 6 months were enrolled. The patients were followed up prospectively until the time point of analysis (November 2016).

The following data were noted before EST: age, sex, liver function test results, physical findings and subjective symptoms, gallbladder and bile duct status, and history of other diseases.

Endoscopic treatment

EST was performed as previously described.[2] All ERCP procedures were performed by experienced endoscopists and generally assisted by a fellow trainee. During the initial ERCP, the presence or absence of a peripapillary diverticulum was recorded. The CBD diameter at its widest point and the size, quantity, and properties of stones were evaluated on cholangiography. After stone removal, balloon occlusion radiography was performed to confirm the clearance of stones. When the stones could not be cleared during the first session, we placed stents and repeated the radiographic examination and ERCP to ensure complete stone removal. For each step, the patient's treatment and clinical course were prospectively assessed and recorded in our database system.

Definitions

The gallbladder and bile duct status were assessed by the patient's history and radiological visualization findings. The gallbladder status referred to the findings of the gallbladder in situ or cholecystectomy. The bile duct status referred to the findings of biliary surgery (biliary exploration combined with T-tube drainage). The quantity and size of the CBDS and diameter of the CBD were determined by endoscopic retrograde cholangiography. The presence/absence of a periampullary diverticulum was determined at the same time. A peripapillary diverticulum was defined as the presence of a diverticulum within a 2-cm radius from the papilla.[3] The presence/absence of pneumobilia was determined by endoscopic retrograde cholangiography after extraction of the stones and was usually performed within 1 week of EST. Pneumobilia was defined as a substantial amount of air in the CBD that was still visualized despite adequate filling of the CBD with contrast and that did not dissipate after changes in the patient's position.[4] A successful procedure was defined as clearance of all stones from the CBD. Complete removal of CBDS was confirmed either by follow-up ERCP or radiological visualization. Early complications were defined as those occurring within 1 month after EST. The severity of early complications was graded according to standardized consensus criteria suggested by Cotton et al.[5] Late complications were defined as those occurring more than 1 month after EST.[4] Recurrence of CBDS was defined as recurrence at least 6 months after previous complete CBDS removal by ERCP.[6] The diagnosis of recurrent CBDS was based on radiological visualization.

Follow-up

The patients were followed up for biliary complications in the outpatient clinic every 2 weeks until their liver function test results became normal and every 3 months thereafter. The follow-up data included biliary symptoms (abdominal pain, jaundice, fever, and chills); laboratory and imaging tests, if performed (liver function tests and abdominal ultrasonography); medical and surgical treatment; and causes of death since the first EST. If symptoms, liver function tests, and/or abdominal ultrasonography indicated possible biliary pathology, the patients were advised to undergo repeat ERCP. The median duration of follow-up was 33.3 months (range, 6–103 months).

Variable selection and data collection

Patient-related and procedure-related factors were considered in the evaluation of risk factors for recurrent CBDS. Patient-related factors were age, sex, gallbladder status, previous biliary surgery, periampullary diverticulum, diameter of the CBD, and size and quantity of the CBDS. Procedure-related factors were precutting, lithotripsy, pneumobilia, complete duct clearance during the first session, and early complications.

Statistical analysis

All statistical analyses were conducted by a statistician using IBM SPSS Statistics, version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ standard deviation and were compared using Student's t-test. Categorical variables were tested using the chi-square test or Fisher's exact test for frequencies that were expected to be low. The cumulative incidence of stone recurrence was calculated by Kaplan–Meier analysis and compared using the log-rank test. Patient-related or procedure-related factors were analyzed to identify predictive risk factors for recurrence after EST. A Cox regression

model was used to determine the most significant factors related to recurrence. A p value of < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 409 patients underwent ERCP, among which 354 achieved successful EST. The remaining 55 patients underwent biliary sphincterotomy plus dilation with a large balloon for bile duct stones because of the large size of the stones ($\geq$20 mm). Seven of the 354 patients died of causes unrelated to EST within 6 months after the procedure (2 died of myocardial infarction, 3 died of cerebrovascular disease, 1 died of chronic lymphocytic leukemia, and 1 died of an accident); these patients were excluded from the study. During the follow-up, two patients were diagnosed with cholangiocarcinoma and excluded. Finally, 345 patients (131 men and 216 women; median age, 63 years; age range, 15–92 years) were included in this long-term study (Figure 1).

Among the 345 patients, 4 (1.15%) had previously undergone gastrectomy (Billroth I in 1 patient, Billroth II in 3 patients), 31 (8.98%) had previously presented with acute cholangitis, and 30 (8.69%) had previously presented with biliary pancreatitis. Before EST, 242 (70.14%) patients had undergone cholecystectomy, among whom 97 (28.11%) had undergone simultaneous biliary duct exploration and T-tube drainage. After EST, 34 (9.80%), had undergone cholecystectomy within 3 months. In the 69 (20.00%) remaining patients with (n = 33) or without (n = 36) CBDS recurrence, the gallbladder was left in situ after EST.

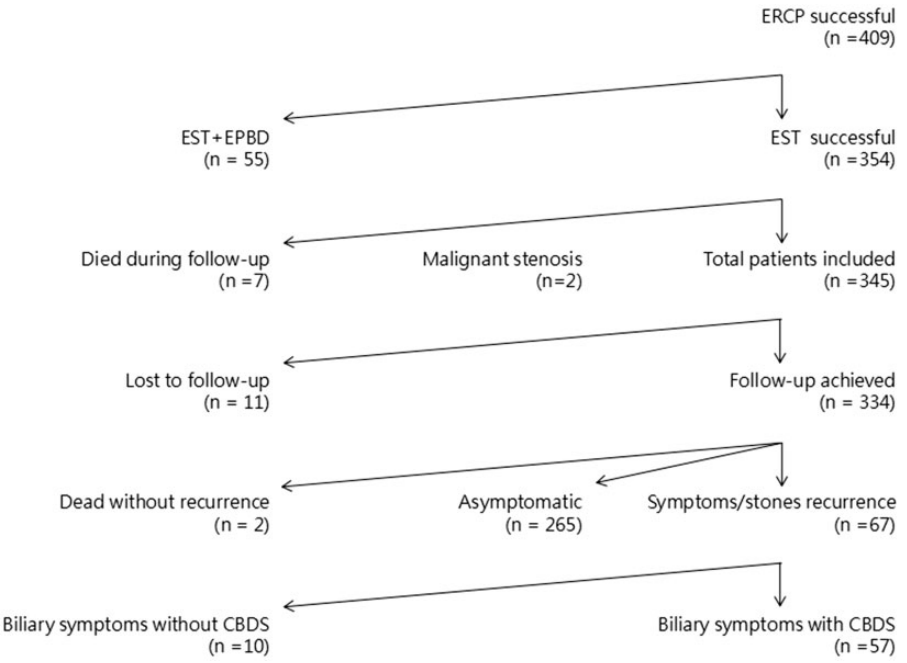

Figure 1. Outcomes in patients undergoing endoscopic sphincterotomy for common bile duct stones. ERCP, endoscopic retrograde cholangiopancreatography; EST, endoscopic biliary sphincterotomy; EPBD, endoscopic papillary balloon dilation.

During EST, a periampullary diverticulum and infundibular fistula were found in 106 (30.72%) and 4 (1.16%) patients, respectively. Precut sphincterotomy and lithotripsy were used in 28 (8.12%) and 67 (19.42%) patients, respectively. The presence of single or multiple stones was found in 138 (40.00%) and 207 (60.00%) patients, respectively. A total of 259 (75.07%) patients achieved complete duct clearance in the first session, while 86 (24.92%) patients were endoscopically cleared after more than one session in our department. Pneumobilia was detected in four patients and evacuated during repeat ERCP. A biliary stent (8–10 Fr) was placed in 44 (12.75%) patients because their stones were too large to be completely cleared in one session, and in 40 patients, the stents were removed after 1 to 3 months and the stones were cleared completely again. During the follow-up, four patients chose to retain the stents because magnetic resonance cholangiopancreatography confirmed the absence of recurrence and they were unwilling to undergo surgical treatment again. The mean CBD diameter on ERCP was 12 mm (range, 2–35 mm), and the mean stone diameter on ERCP was 9 mm (range, 3–23 mm) (Table 1).

Early complications occurred in 37 (10.72%) patients: bleeding in 12 patients, perforation in 1 patient, pancreatitis in 16 patients, and cholangitis in 12 patients (Table 2). Some patients had more than one complication. Two patients had both mild bleeding and mild pancreatitis, and two patients had both mild bleeding and

Table 1. Clinical characteristics of patients and ERCP findings at admission.

Age, years	63 (18–92)
Sex, male/female	129/216
Before EST	
Cholecystectomy	242 (70.14)+ biliary tract surgery, 97 (28.11)
Gastrectomy	4(1.15%),Billroth I, 1 (0.29); Billroth II, 3 (0.86)
Acute cholangitis	31 (8.98)
Biliary pancreatitis	30 (8.69)
During EST	
Periampullary diverticulum	106 (30.72)
Infundibular fistula	4 (1.16)
Precut sphincterotomy	28 (8.12)
Lithotripsy	67 (19.42)
Quantity of CBDS	
Single	138 (40.00)
Multiple	207 (60.00)
Diameter of CBDS, mm	9 (3–23)
Diameter of CBD, mm	12 (2–35)
Complete duct clearance during first session	259 (75.07)
Clearance after more than one session	86 (24.92)
Pneumobilia	4 (1.15)
Biliary stent	44 (12.75); removed, 40 (11.59); retained, 4 (1.15)
After EST	
Cholecystectomy	34 (9.80)
Gallbladder left in situ	69 (20.00)

Data are presented as mean (range), n, or n (%).

ERCP, endoscopic retrograde cholangiopancreatography; EST, endoscopic biliary sphincterotomy; CBD, common bile duct; CBDS, common bile duct stones

mild cholangitis. All complications were mild or moderate. No EST-related death occurred.

Of the 345 patients, 67 developed biliary symptoms during follow-up. These symptoms were attributed to choledochal complications including recurrence (n = 57, 16.52%), acute cholecystitis (n = 2), and acute cholangitis (n = 16) (Table 2). Among the 57 patients with recurrence, cholangitis occurred in 10 patients, 2 of whom developed a liver abscess. Six patients with acute cholangitis underwent repeat ERCP without CBDS recurrence but with papillary stenosis.

Table 2. Complications of endoscopic sphincterotomy in 345 patients.

Complications		n
Early complications	Bleeding	12
	Perforation	1
	Pancreatitis	16
	Cholangitis	12
	Total	37
Late complications	Recurrence	57
	Acute cholangitis	16
	Acute cholecystitis	2
	Liver abscess	2
	Total	65

Risk factors for recurrence

Recurrence of CBDS was detected in 57 patients. Fourteen patients developed recurrence multiple times (twice in 6 patients and three or more times in 8 patients). The median length of time until recurrence was 10.25 months (range, 6–54.4 months). The cumulative recurrence rates at 10, 20, 40, 60, and 80 months in the overall patient population were 8.07% (95% confidence interval [CI], 5.23%–10.97%), 12.68% (95% CI, 9.18%–16.18%), 14.99% (95% CI, 11.24%–18.75%), 16.42% (95% CI,

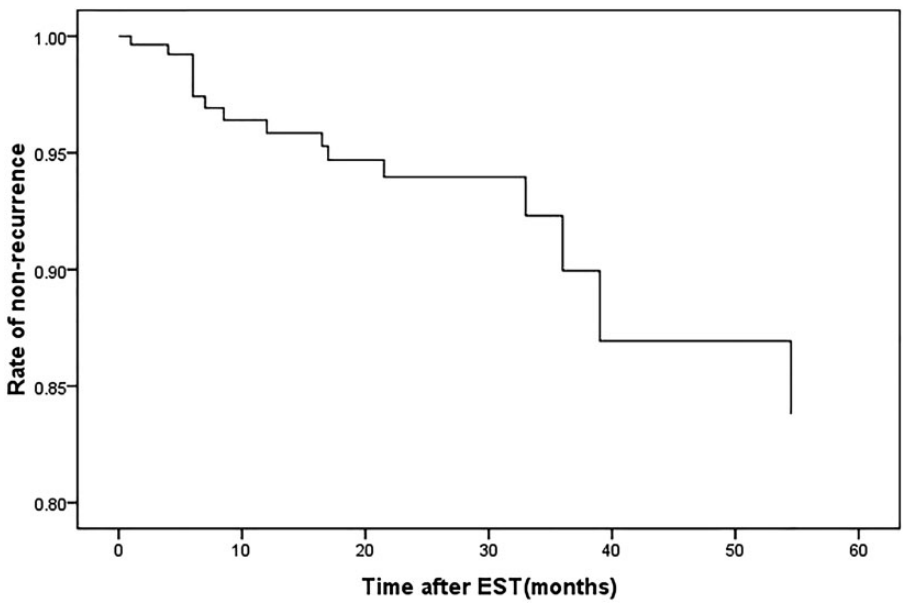

Figure 2. Kaplan–Meier curves for the cumulative rate of recurrence of bile duct stones in patients who underwent successful endoscopic sphincterotomy and stone clearance. EST, endoscopic biliary sphincterotomy.

Table 3. Univariate analysis for recurrence of bile duct stones.

Variables		n	Recurrence	p	RR	(95% CI)
Age, years	≥60	203	32	0.59	0.86	0.51–1.48
	<60	142	25			
Sex	M	129	27	0.16	1.47	0.86–2.51
	F	216	30			
Cholecystectomy prior to EST	Yes	242	17	0.03	0.44	0.22–0.91
	No	103	40			
Gallbladder in situ after EST	Yes	69	17	0.52	0.80	0.40–1.59
	No	276	40			
History of biliary tract surgery	Yes	97	32	0.00	4.01	2.34–6.89
	No	248	25			
Periampullary diverticulum	Yes	106	32	0.02	1.86	1.09–3.17
	No	239	25			
Diameter of CBD, mm	>15	138	38	0.00	2.67	1.49–4.72
	≤15	207	19			
Diameter of CBDS, mm	>8	197	32	0.06	2.45	0.95–6.33
	≤8	148	25			
Quantity of CBDS	>1	207	32	0.02	0.46	0.24–0.89
	1	138	23			
Complete stone removal during first session	Yes	259	30	0.00	0.26	0.15–0.44
	No	86	27			
Lithotripsy	Yes	67	19	0.01	2.10	1.18–3.72
	No	278	38			
Precutting	Yes	28	7	0.49	1.34	0.58–3.14
	No	317	50			
Early complications	Yes	37	11	0.06	1.94	0.98–3.86
	No	308	46			

RR, risk ratio; CI, confidence interval; M, male; F, female; EST, endoscopic biliary sphincterotomy; CBD, common bile duct; CBDS, common bile duct stones

12.53%–20.31%), and 16.42% (95% CI, 12.53%–20.31%), respectively (Figure 2).

The findings recurrent CBDS in relation to each factor as shown in the univariate analysis are given in Table 3. The following patient-related factors were associated with recurrence: gallbladder status, prior biliary tract surgery (bile duct exploration and T-tube drainage) (Figure 3), periampullary diverticulum, diameter of the CBD (>15 vs. ≤15 mm), and quantity of stones. The following procedure-related factors were related to recurrence: complete stone removal in the first session and lithotripsy (Figure 4). No strong intercorrelation was observed among these seven variables ($r < 0.8$).

The risk factors with p values of <0.2 in the univariate analyses and some important clinical factors were included in the multivariate analyses. The final model consisted of two factors: previous biliary tract surgery and lithotripsy (Table 4). These factors reached statistical significance.

Discussion

Although EST has played a central role in the treatment of CBDS for more than 40 years,[1] challenges related to this technique still remain.

Several authors have reported that early postoperative complications, including

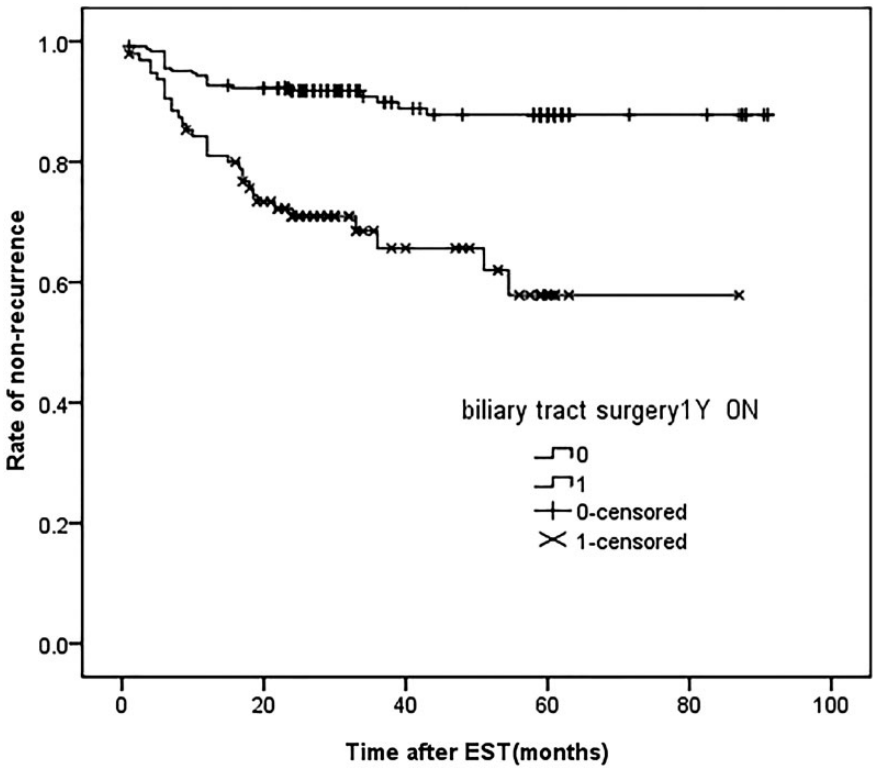

Figure 3. Kaplan–Meier curves showing the rate of stone recurrence in patients classified according to biliary tract surgery. EST, endoscopic biliary sphincterotomy.

bleeding, perforation, acute pancreatitis, and acute cholangitis, occurred in 6.99% to 13.51% of patients.[5,7] Our incidence of early postoperative complications was 10.72%, which was well within the range reported previously. All early complications were mild or moderate, led to no death, and resolved spontaneously within a few days. Therefore, EST was shown to be safe in this study.

In long-term follow-up studies after EST, late postoperative complications were of great concern. Several authors reported that late complications occurred in 11.85% to 20.32% of patients and that recurrence developed in 4% to 24% during follow-up intervals of up to 15 years.[4,8,9] A recent study in China showed that the short-term ($\leq$3 years), long-term (>3 years), and total recurrence rates in the EST group were 13.2%, 6.9%, and 20.1%, respectively.[10] Sugiyama and Atomi[8] reported that two independent risk factors for choledochal complications were a CBD diameter of $\geq$15 mm and brown pigment stones at the initial EST. Natsui et al.[9] reported that bactobilia and gallbladder stones in situ were independent risk factors for late complications. Doi et al.[11] found that the incidence of CBDS recurrence was 15.0% and that the recurrence rate was low in patients who underwent cholecystectomy.

In the present study, the incidence of CBDS recurrence during the follow-up period was 16.52% (57/345), which is comparable with that in other studies. Compared with the single recurrence rate

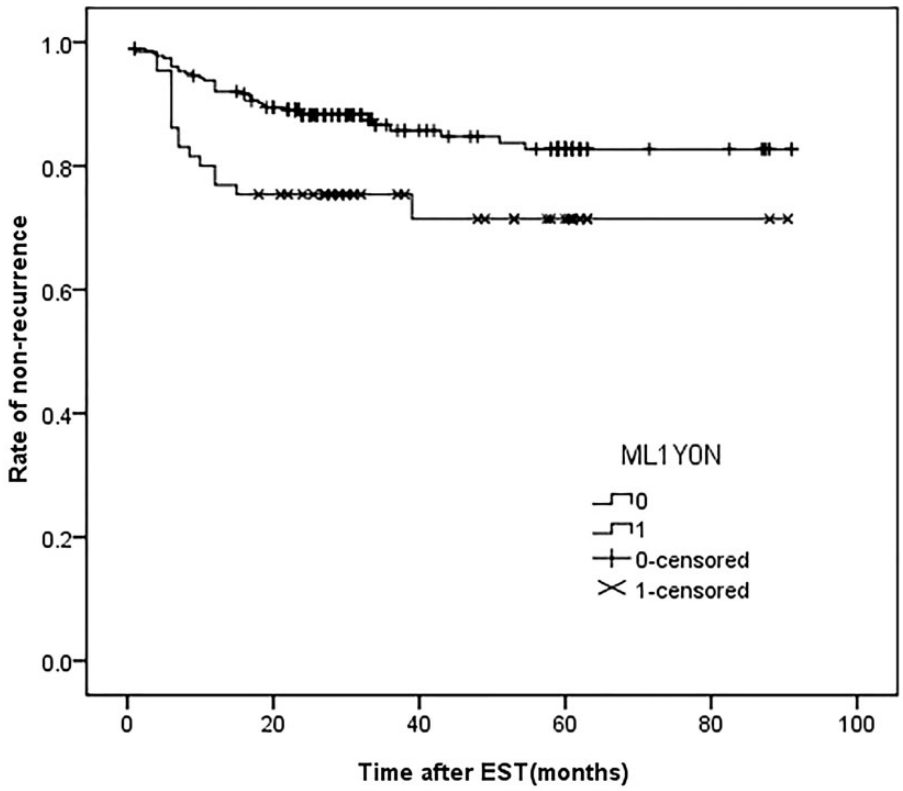

Figure 4. Kaplan–Meier curves showing the rate of stone recurrence in patients requiring or not requiring lithotripsy. EST, endoscopic biliary sphincterotomy.

Table 4. Multivariate analysis of risk factors for recurrent bile duct stones.

Variables			n		Recurrence		p	RR	(95% CI)
History of biliary tract surgery	Yes	No	97	248	32	25	0.01	5.69	1.35–24.05
Lithotripsy	Yes	No	66	279	19	38	0.04	3.34	1.04–10.78

RR, risk ratio; CI, confidence interval

of 12.46% (43/347), multiple recurrences were observed in 4.05% (14/347) of all patients and three or more occurrences were found in 14.04% (8/57) of patients. Therefore, patients with two previous occurrences of CBDS should be carefully followed up, and surveillance endoscopic retrograde cholangiography should be recommended.[4]

In the multivariate analysis, we found that prior biliary tract surgery and lithotripsy were independent risk factors for recurrence.

Patients in the present study who had undergone a prior biliary tract surgery (bile duct exploration and T-tube drainage) had a higher incidence (57.89%) of recurrence than those without such a history. It is conceivable that biliary manipulation could lead to an oblique CBD (OCBD) by introduction of local adhesions.

Strnad et al.[12] indicated that an OCBD was more often observed in patients who had previously undergone an intervention involving the biliary tree. An OCBD could compromise the motility of the biliary tract, reduce bile flow, and induce biliary stasis. Seo et al.[13] found that T-tube drainage influenced bile duct angulation and the change in the sum of the angles before and after T-tube drainage and suggested that the bile duct angulation and the performance of T-tube choledochostomy may be risk factors for recurrence of CBDS. Keizman et al.[14] indicated that patients with a sharp CBD angulation ($\leq 145°$) had a relative risk of 5.2 for stone recurrence by cholangiographic angulation compared with those with an angle exceeding 145°. Bile duct angulation might cause bile stasis, which is thought to be an important factor in the pathogenesis of CBDS.[15]

Lithotripsy was also related to the development of recurrent stones in this study. Previous studies have indicated that small stone fragments left after lithotripsy might act as niduses for stone recurrence.[4,16] Saito et al.[17] considered that larger stones (>11 mm in diameter) were more likely to recur because most of these stones were cleared by lithotripsy. In the present study, if the stones were not removed during the first session after lithotripsy, stents were placed for adequate drainage of biliary sludge, and the residual stones were subsequently confirmed by cholangiography and removed. Therefore, it is important to flush out minute fragments from the CBD. If small fragments are completely cleared from the CBD, the recurrence rate might decrease.[4] Segmental balloon closure radiography was effective to confirm the clearance of stone fragments.

Limitations

This study had several limitations, including its retrospective, single-center design and relatively small sample size. This study could be improved by both a larger sample size and a follow-up period of >5 years. A prospective multicenter cohort study is needed to further investigate the association between these risk factors and stone recurrence.

Conclusions

Most patients with CBDS who achieved EST and stone clearance had no further severe biliary events during the follow-up period. Patients who have previously undergone biliary tract surgery or lithotripsy should be followed up on a regular schedule after the initial EST. In patients with multiple recurrences, repeat ERCP is a reasonable treatment.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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