

# Analysis of symptomatic recurrences of common bile duct stones after endoscopic removal

## Factors related to early or multiple recurrences

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### Abstract

Early or multiple recurrences of symptomatic common bile duct (CBD) stones are troublesome late complications after endoscopic stone removal. We aimed to determine the factors related to early or multiple recurrences of CBD stones.

We retrospectively analyzed patients who underwent endoscopic CBD stone extraction in a single institute between January 2006 and December 2015. Patients were divided into 2 groups according to the number and interval of CBD stone recurrences: single versus multiple ( $\geq 2$ ) and early ( $< 1.5$  years) versus late ( $\geq 1.5$  years) recurrence.

After exclusion, 78 patients were enrolled and followed up for a median of 1974 (IQR: 938–3239) days. Twenty-seven (34.6%) patients experienced multiple recurrences ( $\geq 2$  times), and 26 (33.3%) patients experienced early first recurrence ( $< 1.5$  years). In the multivariate analysis, CBD angulation was independently related to multiple CBD stone recurrence (OR: 4.689,  $P = .016$ ), and endoscopic papillary large balloon dilation was independently related to late first CBD stone recurrence (OR: 3.783,  $P = .025$ ). The mean CBD angles were more angulated with increasing instances of recurrence (0, 1, 2, 3, and  $\geq 4$  times) with corresponding values of  $150.3^\circ$ ,  $148.2^\circ$ ,  $143.6^\circ$ ,  $142.2^\circ$ , and  $126.7^\circ$ , respectively ( $P = .011$ ). The period between the initial treatment and first recurrence was significantly longer than the period between the first and second recurrence ( $P = .048$ ).

In conclusion, greater CBD angulation is associated with the increased number of CBD stone recurrence, and EPLBD delays the recurrence of CBD stones after endoscopic CBD stone removal.

**Abbreviations:** CBD = common bile duct, CI = confidence interval, EPLBD = endoscopic papillary large balloon dilation, ERCP = endoscopic retrograde cholangiopancreatography, IQR = interquartile range, OR = odds ratio, SD = standard deviation, UDCA = ursodeoxycholic acid.

**Keywords:** choledocholithiasis, common bile duct, endoscopic retrograde cholangiopancreatography, recurrence

## 1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) has been adopted as a standard treatment for common bile duct

(CBD) stones since the introduction of endoscopic sphincterotomy.<sup>[1]</sup> ERCP is a minimally invasive procedure that allows patients to recover earlier than surgery or percutaneous transhepatic biliary drainage. As more ERCP procedures have been performed for CBD stones, recurrence of CBD stones has become a well-established troublesome late complication.<sup>[2]</sup> Although the incidence of recurrent CBD stones after ERCP varies according to studies, the reported incidence is 7% to 21%, which is not uncommon.<sup>[2–5]</sup> Several studies, including our previous study, have evaluated the factors related to CBD stone recurrence.<sup>[4,6–8]</sup> Related probable risk factors are multiple or large CBD stones, intrahepatic stones, pneumobilia, dilated or sharp angles of the CBD, gallstones in the gallbladder in situ, delayed biliary emptying, periampullary diverticulum, duodenobiliary reflux, papillary or biliary stricture, systemic disease (e.g., hemolytic anemia), and so on. Although the risk factors associated with CBD stone recurrence have been studied, those related to early or multiple recurrences have not been studied thus far. Therefore, we focused on the interval and multiplicity of CBD stone recurrences and aimed to determine which characteristics are related to early or multiple recurrences in patients who underwent endoscopic CBD stone removal.

## 2. Material and methods

### 2.1. Patients

Patients who underwent CBD stone removal by ERCP in a single institute between January 2006 and December 2015 were

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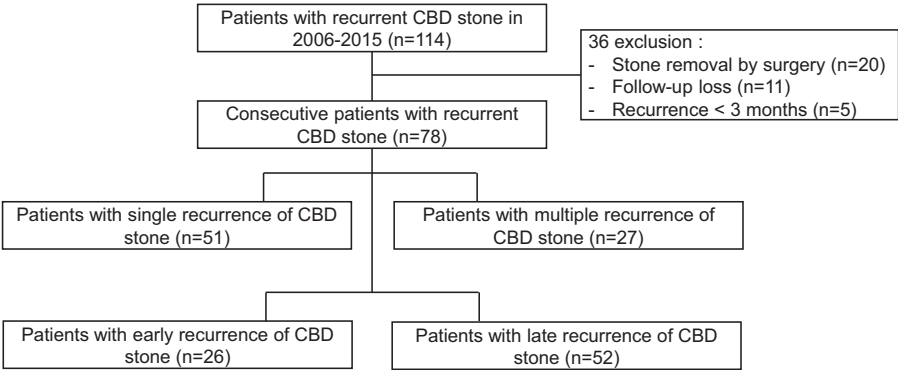


Figure 1. Flowchart of patient groups.

evaluated. Among them, 114 patients encountered recurrence of CBD stones within the follow-up period. We performed magnetic resonance cholangiopancreatography (MRCP) (n=71) and/or abdominal ultrasonography (n=31) for patients to confirm the existence of gallbladder stone. CT scan was performed for all patients (n=78). Thirty-six patients were excluded from this study due to surgical removal of CBD stones during follow-up (n=20), follow-up loss (n=11), and recurrence less than 3 months after ERCP (n=5) (Fig. 1). Finally, 78 patients were enrolled and divided into two groups based on recurrence number and period: single versus multiple ( $\geq 2$  times) recurrence and early ( $< 1.5$  years) versus late ( $\geq 1.5$  years) recurrence. For comparison of CBD angles with the recurrence group, 59 patients without recurrence, who underwent endoscopic CBD stone removal between 2010 and 2012 and were followed up until 2020, were consecutively selected.

2.2. Endoscopic extraction of common bile duct stones

ERCP was performed with a duodenoscope (JF 260; Olympus Optical Co., Ltd., Tokyo, Japan). All patients underwent endoscopic sphincterotomy prior to stone extraction. Papillary balloon dilation was considered for the patients with large CBD stones ( $\geq 10$  mm), periampullary diverticulum, or bleeding tendency. Endoscopic papillary large balloon dilation (EPLBD) (10–18 mm) was executed with a controlled radial expansion balloon dilator (CRE; Boston Scientific Co., Natick, MA). The CBD stones were extracted with a basket and/or a retrieval balloon catheter. When a stone basket was trapped by a large stone, a mechanical lithotripsy was performed. To exclude residual stones after ERCP stone removal, we placed an endoscopic nasobiliary drainage catheter and performed a follow-up cholangiogram the day after the procedure in case of multiple CBD stones.

2.3. Clinical information and definitions

We retrospectively interrogated the patients’ clinical information from the archived computer databases. Whenever hospitalized for a procedure, the patient’s clinical information, such as age, sex, underlying disease, and use of medication, was recorded and reinforced prospectively on our computerized charts. A CBD angle was estimated on fluoroscopic images using the ViewRex viewer program as the most acute angle along the CBD from the bifurcation to the papilla as introduced by Keizman (Fig. 2).<sup>[9]</sup>

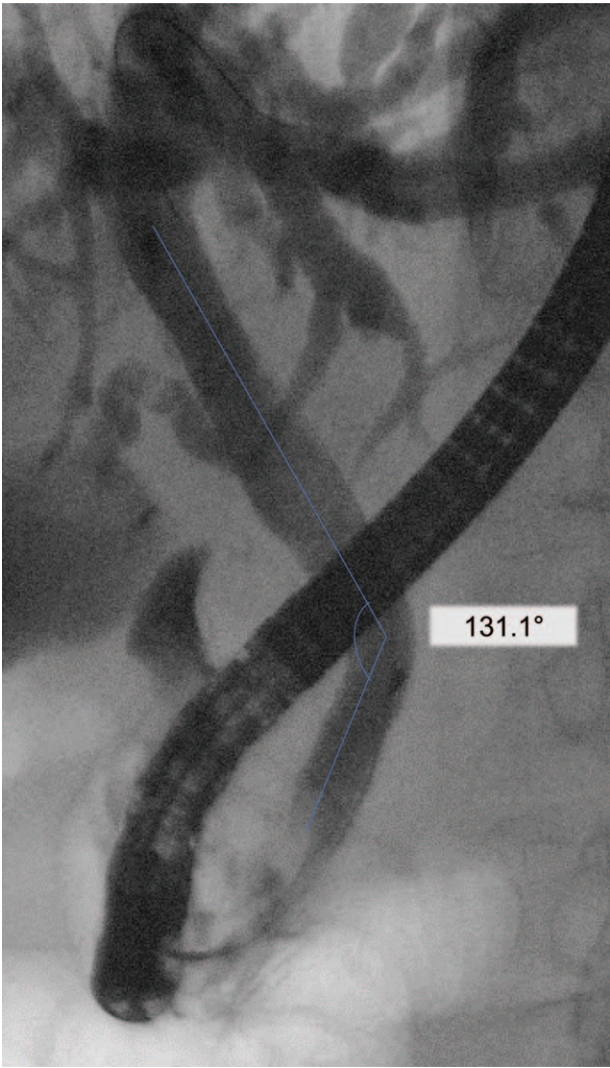


Figure 2. Measurement of common bile duct angle.

The CBD diameter was determined by estimation of the largest diameter of the CBD on coronal images of MRCP or CT scans. Additionally, the size and number of CBD stones were measured in the same manner. EPLBD was defined as dilation of the major ampulla by the balloon with a diameter greater than 10 mm. The

classification of periampullary diverticulum was divided into types 1 (intradiverticulum), 2 (diverticular margin), and 3 (extradiverticulum) as the location of the major ampulla relative to the diverticulum.<sup>[10]</sup>

#### 2.4. Ethics statement

A patient's anonymity was carefully protected, and all study protocols were in complete compliance with the declaration of Helsinki. Ethics committee approval was received for this study from the Institutional Review Board of Bucheon St. Mary's hospital (No. HC20RISI0110).

#### 2.5. Statistical analysis

Categorical clinical data from the two groups are expressed as numbers and percentages and were compared with Pearson's chi-square test. Continuous clinical data are shown as the mean  $\pm$  standard deviation or median  $\pm$  interquartile range and were compared with Student's *t* test or one-way ANOVA. In multivariate analysis for determination of the factors associated with early or multiple recurrence of CBD stones, logistic regression analysis (enter method) was conducted on both patient-related and ERCP-related variables. The odds ratios and 95% confidence intervals were calculated. A *P* value  $< .05$  was regarded to be significant. All statistical analyses were performed using SPSS version 20 (SPSS, Inc., Chicago, IL).

### 3. Results

#### 3.1. Baseline characteristics

The mean age of the patients when CBD stones first occurred was 66.5 (range: 48–83), and the male/female ratio was 40/38 (51%/

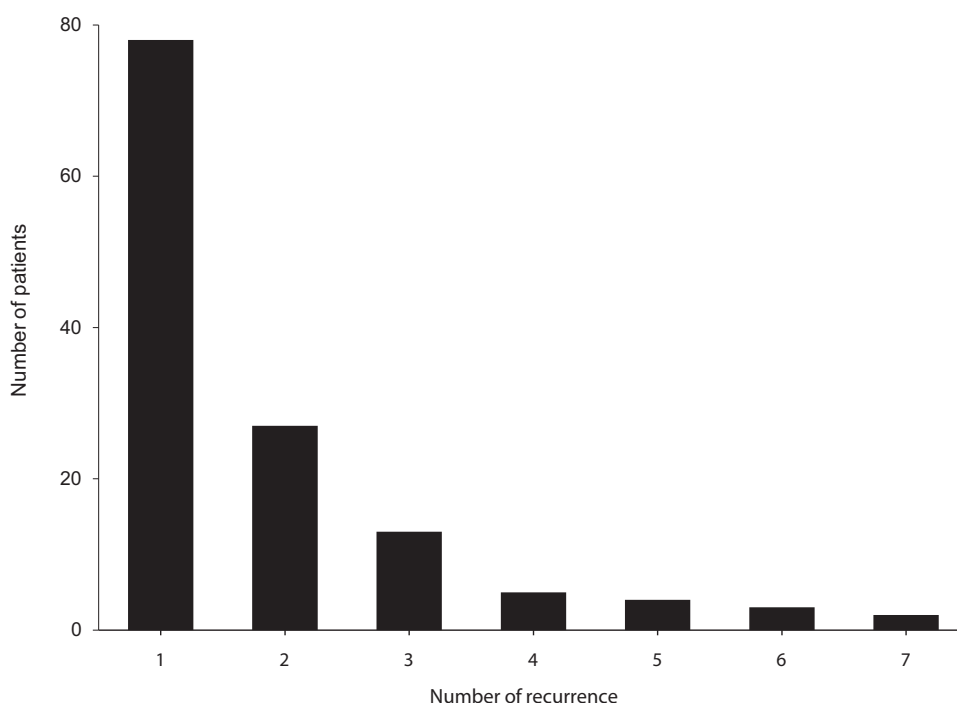
**Table 1**

**Baseline characteristics of patients with recurrent common bile duct stones.**

Characteristics	n = 78
Age, mean $\pm$ SD	66.5 $\pm$ 11.9
Male	40 (51.3%)
Alcohol	15 (19.2%)
Smoking	12 (15.4%)
Diabetes	21 (26.9%)
Hypertension	41 (52.6%)
Cholecystectomy	
Overall	53 (67.9%)
Previous	23 (39.5%)
Billroth subtotal gastrectomy	1 (5.1%)
Follow-up duration, median (IQR), days	1974 (938–3239)

IQR = interquartile range.

49%) (Table 1). Regarding comorbidity, 41 (53%) patients had hypertension and 21 (27%) had diabetes. The patients were followed up for a median of 1974 (IQR 938–3239) days. Cholecystectomy was performed in 53 (68%) patients. It was performed before enrollment in 23 (29%) patients and after enrollment in 30 (38%) patients. Among 78 patients with recurrence, 27 (34%) patients experienced multiple recurrences ( $\geq 2$  times) of CBD stones. Fifth, sixth, and seventh recurrences were observed in 4 (5%), 3 (4%), and 2 (3%), respectively (Fig. 3). Of the 78 patients with recurrent CBD stones, 35 patients underwent ERCP twice, 19 underwent ERCP three times, 10 underwent ERCP 4 times, 6 underwent ERCP 5 times, 4 underwent ERCP 6 times, and 4 underwent ERCP more than 7 times. The maximum number of ERCPs in 1 patient was 11.



**Figure 3.** Numbers of patients according to the total number of recurrences during the follow-up period.

**Table 2****Comparison between the single and multiple recurrence groups.**

	CBD stone recurrence		P
	Single (n=51)	Multiple (n=27)	
Age, mean $\pm$ SD (yr)	67.7 $\pm$ 12.0.	64.2 $\pm$ 11.6	0.213
Male	28 (55%)	12 (44%)	0.379
Follow-up time, mean $\pm$ SD (days)	1877 $\pm$ 1557	1857 $\pm$ 1498*	0.957
Gallbladder stone <sup>†</sup>	8 (16%)	2 (7%)	0.480
Cholecystectomy			
Prior to ERCP	14 (28%)	9 (33%)	0.588
Overall	32 (63%)	21 (78%)	0.176
Billroth subtotal gastrectomy	3 (6%)	1 (4%)	1.000
UDCA and/or Rowachol medication	44 (86%)	26 (96%)	0.250
<b>Initial ERCP findings</b>			
Intrahepatic stones	5 (10%)	8 (30%)	0.025
No. of CBD stones			0.352
1	19 (37%)	13 (48%)	
$\geq 2$	32 (63%)	14 (52%)	
Size of the largest CBD stone, mean $\pm$ SD (mm)	10.5 $\pm$ 5.8	12.2 $\pm$ 9.5	0.340
<15	37 (73%)	18 (67%)	0.588
$\geq 15$	14 (27%)	9 (33%)	
CBD diameter, mean $\pm$ SD (mm)	15.6 $\pm$ 4.7	17.5 $\pm$ 5.3	0.110
<15	24 (47%)	11 (41%)	0.594
$\geq 15$	27 (53%)	16 (59%)	
CBD angle, mean $\pm$ SD (°)	148.2 $\pm$ 13.1	140.1 $\pm$ 16.0	0.019
<135	5 (10%)	9 (33%)	0.010
$\geq 135$	46 (90%)	18 (67%)	
EPLBD	23 (45%)	10 (37%)	0.493
Size of papillary balloon dilation, mean $\pm$ SD (mm)	12.6 $\pm$ 2.8	12.8 $\pm$ 2.7	0.850
Mechanical lithotripsy	2 (4%)	2 (7%)	0.606
Periampullary diverticulum			0.234
None	17 (33%)	11 (41%)	
Type 1	8 (16%)	7 (26%)	
Type 2	10 (20%)	6 (22%)	
Type 3	16 (31%)	3 (11%)	
CBD stricture	0 (0%)	1 (4%)	0.351
More than one ERCP to clear CBD	8 (16%)	4 (15%)	1.000
Post-ERCP complication	6 (12%)	6 (22%)	0.223

CBD=common bile duct, EPLBD=Endoscopic papillary large-balloon dilation, ERCP=endoscopic retrograde cholangiopancreatography, SD=standard deviation, and UDCA=ursodeoxycholic acid.

\* Until the second recurrence.

<sup>†</sup> In patients without cholecystectomy during follow-up.

### 3.2. Single versus multiple recurrences of common bile duct stones

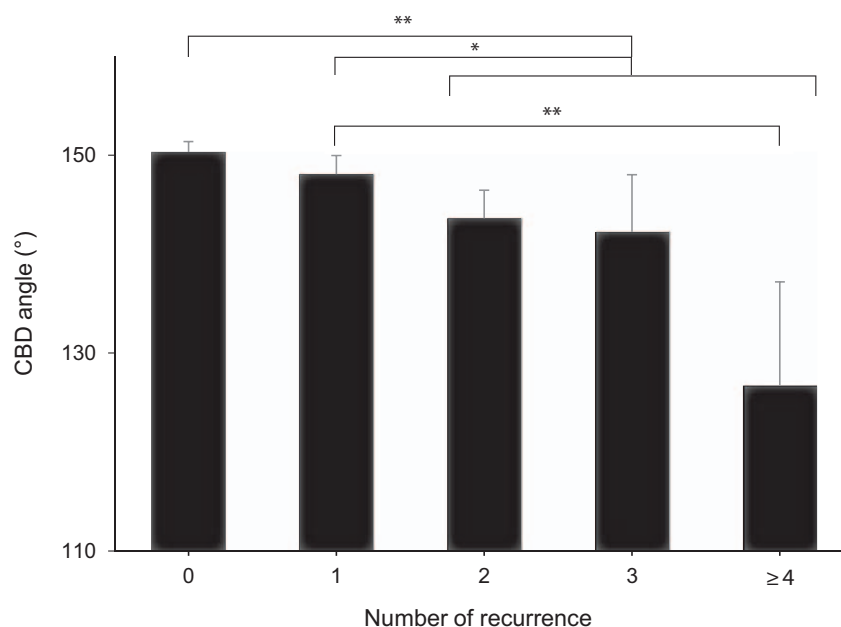
Fifty-one (65%) patients experienced a single recurrence of CBD stones, and 27 (35%) patients experienced multiple recurrences ( $\geq 2$  times). Age, sex, gallbladder stones, cholecystectomy, use of ursodeoxycholic acid, number and size of CBD stones, CBD diameter, EPLBD, and periampullary diverticulum, post-ERCP complications did not differ between the single and multiple recurrence groups (Table 2). However, CBD was more angulated in the multiple recurrence group than in the single recurrence group ( $140.1^\circ \pm 16.0$  vs  $148.2^\circ \pm 13.1$ ,  $P=.019$ ). Moreover, patients with more recurrences had more oblique CBDs: the mean CBD angles according to recurrence numbers (0, 1, 2, 3, and  $\geq 4$  times) were  $150.3^\circ$ ,  $148.2^\circ$ ,  $143.6^\circ$ ,  $142.2^\circ$ , and  $126.7^\circ$ , respectively ( $P=.011$ ) (Fig. 4). In comparison with the no recurrence group, the CBDs of patients with multiple recurrences were significantly more oblique than the CBDs of patients without recurrence ( $140.1^\circ$  vs  $150.3^\circ$ ,  $P=.001$ ). Intrahepatic stones was also more common in the multiple recurrence group than in the single recurrence group (30% vs 10%,  $P=.025$ ). In the multivariate analysis, angulated CBD ( $<135^\circ$ )

and intrahepatic stones were independently related to multiple recurrences of CBD stones (OR: 4.689, 95% CI: 1.331–16.52,  $P=.016$  and OR: 3.962, 95% CI: 1.091–14.40,  $P=.036$ ) (Table 3). For post-procedural complications, one patient had post-ERCP bleeding, and 11 patients developed mild post-ERCP pancreatitis.

### 3.3. Early versus late recurrence of common bile duct stones

Twenty-six (33%) patients experienced early first recurrence ( $<1.5$  years) and 52 (67%) patients experienced late first recurrence ( $\geq 1.5$  years). Age, sex, gallbladder stones, cholecystectomy, use of ursodeoxycholic acid, intrahepatic stones, number and size of CBD stones, diameter and angle of CBD, and periampullary diverticulum did not differ between the early and late first recurrence groups (Table 4). However, EPLBD was performed at a higher rate in the late recurrence group (52%) than in the early recurrence group (23%) ( $P=.015$ ). In the multivariate analysis, only EPLBD was significantly related to late recurrence (OR: 3.783, 95% CI: 1.183–12.098,  $P=.025$ ) (Table 5).





**Figure 4.** Mean angles of the common bile duct according to recurrence number. Error bars indicate standard errors. \* $P < .05$  and \*\* $P < .01$ .

**Table 3**

**Multivariate logistic analysis for multiple recurrences of common bile duct stones.**

Factors	OR (95% CI)	P
Intrahepatic stones (yes vs no)	3.962 (1.091–14.40)	0.036
CBD angle (<135° vs ≥135°)	4.689 (1.331–16.52)	0.016

CBD=common bile duct, CI=confidence interval, and OR=odds ratio.

### 3.4. Recurrence interval based on the number of recurrence events

The mean interval between the initial to the first recurrence was  $1148 \pm 128.5$  days. This was significantly longer than that between the first and second recurrence ( $623 \pm 740$  days,  $P = .048$ ) (Fig. 5). The recurrence intervals after the second recurrence did not differ significantly, but have a tendency to shorten.

## 4. Discussion

CBD stones may recur even though complete removal of CBD stones by ERCP. Unfortunately, some patients experience multiple recurrences and a short recurrence interval. In these cases, the patients suffer from multiple procedures and a high healthcare cost burden.

Multiple recurrences of CBD stones have been reported in a few previous studies. Nzenza et al showed that 51% (26/51) of patients with recurrent CBD stones required three or more ERCP procedures, and up to 11 ERCP procedures were performed for the removal of CBD stones in a single patient.<sup>[2]</sup> Konstantakis et al reported that multiple recurrences occurred in 33% of patients, and the maximum number of ERCP sessions was 6 in 1 patient.<sup>[7]</sup> Our study presented that multiple recurrences occurred in 27 (35%) patients, and the maximum number of recurrences of CBD stones was 8 in 1 patient.

In the present study, multiple recurrences were related to CBD angle and intrahepatic duct stones in univariate analysis, and both were independently related to multiple recurrences in multivariate analysis. CBD angulation was associated with recurrence of CBD stones in the previous studies.<sup>[9,11,12]</sup> Theoretically, angulated CBD may interfere with the flow of bile, and it is a favorable condition for the formation of primary CBD stones. Moreover, our study showed that more multiple recurrences occur in patients with more angulated CBDs, which suggests that patients with more angulated CBDs require special attention and careful follow-up. In terms of angulated CBD, previous studies used criteria of angulated CBD as 145° or 135°.<sup>[9,12]</sup> Our study chose CBD angle of 135° as the criterion of angulated CBD to maximize the difference between the 2 groups.

Early recurrence is another troublesome problem for both clinicians and patients alike. Although the definition of early recurrence has not been established, the first recurrence within a year or 2 is considered early recurrence.<sup>[7]</sup> We defined early recurrence as recurrence within 1.5 years as approximately half of the first recurrence interval. Harada et al showed that EPLBD reduced the recurrence of CBD stones by Kaplan–Meier analysis.<sup>[13]</sup> In addition, Ha et al demonstrated that recurrence was lower in patients with perampullary diverticulum and EPLBD treatment.<sup>[14]</sup> Our study revealed that EPLBD was performed significantly more often in the late recurrence group. Although EPLBD was generally performed in patients with perampullary diverticulum or large CBD stones in the present study, perampullary diverticulum or large CBD stones were not related to the recurrence interval. Therefore, EPLBD itself facilitates the flow of bile and can reduce early recurrence of CBD stones or delay the recurrence time after endoscopic removal of CBD stones.

A few studies have reported regarding recurrence interval of CBD stones. Tanaka et al demonstrated that the average time from receiving ERCP to recurrence was 33 months (range, 6–199 months), and most recurrences occurred within 3 years,

**Table 4****Comparison of the early and late recurrence groups according to the first recurrence interval.**

	1 <sup>st</sup> recurrence interval		<i>P</i>
	Early (n=26)	Late (n=52)	
Age, mean ± SD (yr)	66.6 ± 12.0	66.5 ± 12.0	0.968
Male	15 (58%)	25 (48%)	0.423
Gallbladder stone*	5 (19%)	5 (10%)	0.231
Cholecystectomy			
Prior to ERCP	6 (23%)	17 (33%)	0.380
Overall	19 (73%)	34 (65%)	0.493
Billroth subtotal gastrectomy	1 (4%)	3 (6%)	1.000
UDCA and/or Rowachol medication	25 (96%)	45 (87%)	0.257
<b>Initial ERCP findings</b>			
Intrahepatic stones	4 (15%)	9 (17%)	1.000
No. of CBD stones, mean ± SD			
1	11 (42%)	21 (40%)	0.871
≥2	15 (58%)	31 (60%)	
Size of the largest initial CBD stone, mean ± SD (mm)	11.2 ± 9.8	11.1 ± 5.7	
<15	17 (65%)	38 (73%)	0.926
≥15	9 (35%)	14 (27%)	0.599
CBD diameter, mean ± SD (mm)	16.9 ± 6.0	15.9 ± 4.4	0.435
<15	15 (58%)	20 (38%)	0.107
≥15	11 (42%)	32 (62%)	
CBD angle, mean ± SD (°)	148.2 ± 12.7	144.0 ± 15.4	0.237
<135	5 (19%)	9 (17%)	0.835
≥135	21 (81%)	43 (83%)	
EPLBD	6 (23%)	27 (52%)	0.015
Size of papillary balloon dilation, mean ± SD (mm)	12.9 ± 2.7	12.6 ± 2.7	0.802
Mechanical lithotripsy	2 (8%)	2 (4%)	0.597
Periampullary diverticulum			0.868
None	8 (31%)	20 (38%)	
Type I	6 (23%)	9 (17%)	
Type II	5 (19%)	11 (21%)	
Type III	7 (27%)	7 (13%)	
CBD stricture	0 (0%)	1 (2%)	1.000
More than one ERCP to clear CBD	2 (8%)	10 (19%)	0.318
Post-ERCP complication	6 (23%)	6 (12%)	0.183

CBD = common bile duct, EPLBD = Endoscopic papillary large-balloon dilation, ERCP = endoscopic retrograde cholangiopancreatography, SD = standard deviation, and UDCA = ursodeoxycholic acid.

\* In patients without cholecystectomy during follow-up.

with 13 (30%) patients experiencing recurrence after 5 years and 5 (11%) patients experiencing recurrence after more than 10 years.<sup>[15]</sup> Konstantakis et al reported that the first recurrence interval was 35 ± 17 months, the second recurrence interval was 35 ± 23 months, and the third recurrence interval was 17 ± 15 months.<sup>[7]</sup> Our study showed that the mean interval until the first recurrence was 38 months. This is similar to previous studies, reported as 33 and 35 months. The second recurrence interval (21 months) was significantly shorter than the first recurrence interval. Then, there were no differences of recurrence interval after the second recurrence. A previous study reported that the period between initial and first recurrence (4.4 years) was longer than the period between the first and second recurrence (3.4

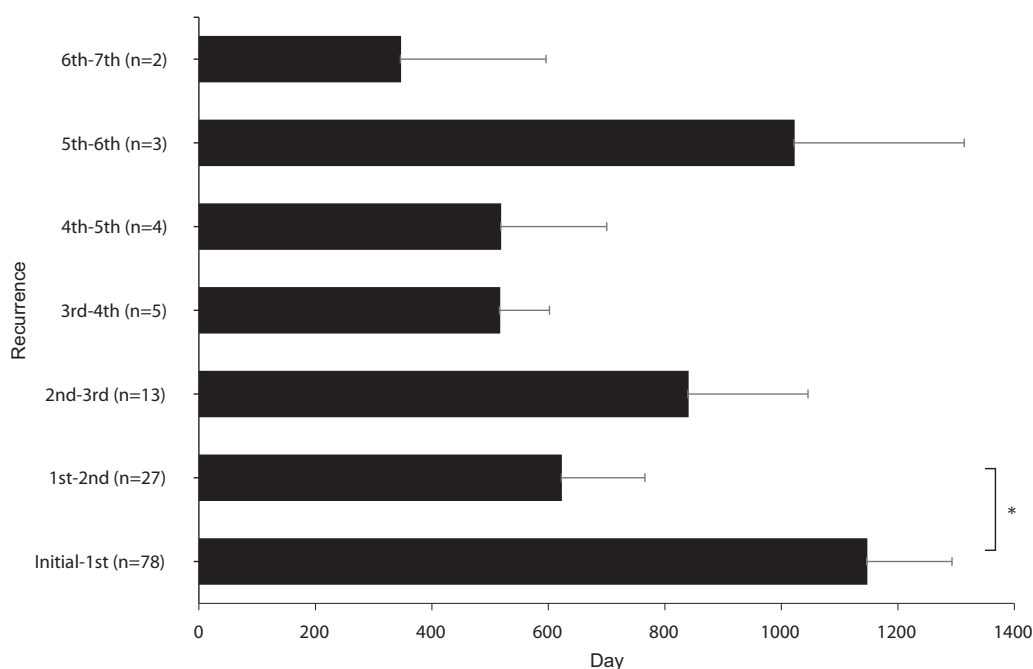
years).<sup>[16]</sup> Furthermore, a third recurrence occurred relatively frequently (10%) and early (3.0 years). This may indicate that the recurrence interval becomes shorter after the first recurrence, as shown by our results.

Biliary stone formation is associated with multiple factors. One study involving 43,141 twin pairs showed that genetic effects, shared environmental effects, and unique environmental effects accounted for 25%, 13%, and 62% of gallstones, respectively.<sup>[17]</sup> As genetic factors, several gallstone-predisposing gene mutations have been reported, such as mutations of ABCB4 and ABCG5/G8 genes.<sup>[18,19]</sup> Among non-genetic factors, biliary stasis (delayed biliary emptying and/or impaired biliary flow) is an important factor in the pathogenesis of bile duct stone. CBD angulation, CBD dilation, periampullary diverticula, biliary strictures, papillary stenosis, and cholecystectomy have been associated with biliary stasis.<sup>[7]</sup> Angulation along CBD may predispose an individual to bile stasis, leading to higher bile concentration and increase of cholesterol saturation. This could promote stone formation and recurrence as demonstrated in a meta-analysis of eight randomized trials (1776 patients).<sup>[20]</sup> Since there is still a lack of basic research on bile kinetics, further studies on bile kinetics are needed to clarify the pathogenesis of bile duct stone formation.

**Table 5****Multivariate analysis for the first recurrence interval of common bile duct stones.**

Factors	OR (95% CI)	<i>P</i>
CBD diameter (≥15 mm vs <15 mm)	1.270 (0.430–3.751)	0.666
EPLBD (yes vs no)	3.783 (1.183–12.10)	0.025

CBD = common bile duct, CI = confidence interval, EPLBD = endoscopic papillary large-balloon dilation, and OR = odds ratio.



**Figure 5.** Mean recurrence interval according to recurrence number. Error bars indicate standard errors. \* $P < .05$ .

There are limitations in the present study. First, the study has a retrospective design. A few data points could have been missed, and some further data collection could not be performed due to the study design. Second, it might not be completely excluded that there are secondary or residual stones after ERCP. In patients with gallbladders in situ, old or newly developed gallstones can migrate to the CBD and become secondary CBD stones. In our study, cholecystectomy was performed in 53 (68%) patients and gallbladder stones were in 10 (13%) patients. However, cholecystectomy or gallbladder stones was not associated with the interval or multiplicity of CBD stone recurrence. Therefore, secondary CBD stones might be few in number, so the effects were minimal in the present study. Regarding residual CBD stones, we excluded patients who had recurrence within 3 months after ERCP and confirmed that there were no residual CBD stones by endoscopic nasobiliary drainage catheter cholangiography the day after ERCP in patients with multiple CBD stones. It might exclude the residual stones in our study. Third, intrahepatic duct stones as well as CBD angle were associated with multiple recurrences in the present study. Since intrahepatic duct stones are very rare in European and North American populations, this result may be more relevant for Asiatic ethnicity.

In conclusion, greater CBD angulation is associated with the increased number of CBD stone recurrence, and EPLBD delays the recurrence time of CBD stones after endoscopic extraction in patients with recurrent CBD stones. We expect a further study with a large number of patients in the near future.

### Author contributions

**Conceptualization:** Jae Hyuck Chang.

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**Writing – review & editing:** Soo Jeong Han, Jae Hyuck Chang, Hyung-Keun Kim.

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