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Identification of risk factors involved in recurrence after common bile duct stone removal with ERCP

A retrospective observational study

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Abstract

Recurrent stone detection is common after endoscopic treatment of common bile duct stones (CBDS). This study aimed to identify the risk factors for recurrence of CBDS.

We retrospectively evaluated 14 patients who underwent endoscopic treatment for CBDS. Risk factors for single and multiple recurrent CBDSs were evaluated using logistic regression analysis.

Endoscopic and needle-knife precut sphincterotomy was performed in 506 and 112 patients, respectively. There was 1 recurrence in 85 patients (13.8%), 2 recurrences in 23 patients (3.7%), and 3 recurrences in 9 patients (1.5%). According to the multivariate analyses, being older than 65 years (odds ratio [OR] 1.084, $P = .000$), concomitant heart disease (OR 2.528, $P = .002$), concomitant lung disease (OR 1.766, $P = .035$), a large common bile duct diameter (OR 1.347, $P = .000$), presence of cholelithiasis (OR 1.752, $P = .018$), stent (OR 1.794, $P = .023$), or T-tube placement in the common bile duct (OR 47.385, $P = .000$), and prolongation of the procedure (OR 1.037, $P = .000$) increased the risk of recurrence, while having undergone cholecystectomy due to gallstones (OR 1.645, $P = .042$). The mean stone diameter ($P = .059$), nitroglycerin use ($P = .129$), and periampullary diverticulum ($P = .891$) did not increase the risk of recurrent CBDS.

The probability of multiple recurrences after the first recurrence of CBDS increased with age >65 years, concomitant heart/lung diseases, stent/T-tube placement in the common bile duct, a wide common bile duct (≥10 mm), and cholelithiasis.

Abbreviations: CBDS = common bile duct stones, CI = confidence interval, CNS = central nervous system, EPBD = endoscopic papillary balloon dilatation, EST = endoscopic sphincterotomy, GBS = gall bladder with stones, OR = odds ratio, PAD = periampullary diverticulum.

Keywords: common bile duct gallstone, endoscopic, recurrence, retrograde cholangiopancreatography, risk factors

1. Introduction

Common bile duct stones (CBDS) are the most common biliary tract diseases, and endoscopic retrograde cholangiopancreatography (ERCP) is currently the standard treatment for CBDS due to its minimally invasive nature.[1] Endoscopic sphincterotomy (EST) or endoscopic papillary balloon dilatation (EPBD) are treatments for the removal of CBDS. While EST is very effective for the endoscopic treatment of small bile duct stones, advanced treatment methods are needed for hard, large, and multiple stones.[2]

Recently, needle-knife precut sphincterotomy, performed with a needlepoint sphincterotome, as well as endoscopic papillary

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Since the article is a retrospective, observational study, ethics committee approval was not obtained. Institutional permission was obtained from Bandırma Training and Research Hospital to conduct the research.

Written informed consent was obtained from all patients in the study to participate in the study.

Written informed consent was obtained from all patients included in the study for the publication of personal data.

The study has never been presented anywhere before.

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All relevant data are within the paper and its Supporting information files.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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large balloon dilatation, have been reported as useful techniques for difficult CBDS. However, the needle-knife precut sphincterotomy treatment method, which has a considerable complication risk, is still not widely accepted.[3,4]

Even after complete clearance of the common bile duct, recurrent CBDS is not rare; recurrence rates of 17% have been reported after EST.[5] A gallbladder with stones (GBS) that is left in place and a large common bile duct are risk factors for recurrent CBDS.[6] A recent study found that the incidence of multiple recurrences was high after the first CBDS recurrence; the second and third recurrence rates were 23.4% and 33.4%, respectively.[7] This study aimed to identify risk factors for multiple recurrences after endoscopic removal of CBDS with EST and needle-knife precut sphincterotomy methods and to elucidate effective interventions to prevent further recurrences.

2. Materials and methods

The medical records of 614 patients who received endoscopic treatment for CBDS between April 2015 and February 2021 at a third-level referral hospital were retrospectively reviewed. The exclusion criteria were as follows: having undergone surgical intervention that prevented access to the papilla, cases with nonpapillary drainage (percutaneous transhepatic biliary drainage), cases of malignancy requiring permanent biliary stent, patients with common bile duct stenosis, or coagulopathy, those with incomplete records, and patients whose common bile ducts could not be cleared thoroughly from stones. All patients included in the study signed a consent form for ERCP and related treatment before any procedure. The present study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all patients to participate in the study. Since the article is a retrospective, observational study, ethics committee approval was not obtained. Institutional permission was obtained from Bandirma Training and Research Hospital to conduct the research.

2.1. Technical set-up

ERCP was performed under sedation with topical 10% Xylocain (lidocaine, AstraZeneca, Cambridge, UK) followed by intravenous Aldolan (pethidine HCl, G.L. Pharma GmbH, Lannach, Austria) and Dormicum (midazolam, Roche, Basel, Switzerland). Buscopan (hyposin-N-butyl bromide, Boehringer Ingelheim, Ingelheim, Germany) was used to reduce intestinal peristalsis.

The procedures were performed using a side-viewing duodenoscopic system (XL; Fujinon system, Tokyo, Japan), and synchronous imaging techniques were used to confirm the location of the bile duct (Toshiba E5764SD-P4A, Medison X-ray, Korea). Prophylactic antibiotics were routinely administered to all patients before ERCP.

The procedure was initiated with the classical approach using a standard sphincterotome or a guidewire for patients with a normal-appearing papilla. If cannulation could not be achieved despite the techniques mentioned above after a reasonable time, the case was defined as "failed" and abandoned. We checked the indications and the requirement for the procedure of the patient and repeated the ERCP procedure 3 days after the first attempt.

In the second attempt, the ERCP procedure was initiated with 1 of the 2 methods, depending on the features of the papilla. If the papilla indicated a failed ERCP, the procedure was initiated directly with a precut incision. We proposed a modified technique and certain steps while making a precut to achieve the maximum benefit.

The needle-knife precut technique was performed as follows: biliary access was attempted with a needle-tipped sphincterotome, starting from the orifice of the papilla and making an incision in the cephalad direction (classical method). In this method, the mucosa and submucosa are denuded, and slightly pearlescent bulging sphincters are revealed. Then, the same procedure was applied to the sphincters, the salmon-colored biliary mucosa was opened, and cannulation was performed.

The procedure to be applied after common bile duct cannulation is EST. After EST, the guide wire is detected radiographically in the common bile duct and the duct is visualized by administering contrast material, and then intraluminal stones are cleared with an endoscopic basket or endoscopic balloon according to the existing pathology. Finally, occlusion cholangiography was performed to ensure that there were no stones in the lumen. However, if multiple hard, square-shaped stones that are larger than the balloon endoscope can be captured during the procedure, a plastic stent is placed; the patient is treated with ursodeoxycholic acid and called for an appointment again.

When the first cannulation of the patients failed, nitroglycerin was applied, and the procedure was repeated after 3 days of edema-reducing treatment. The procedure begins with the aim of EST with classical cannulation, but needle-knife precut sphincterotomy is performed in unsuccessful cases of EST. Complications such as bleeding, pancreatitis, and cholangitis were noted, and the patients were followed up in the ward.

Bleeding was defined as at least a two-point decrease in hemoglobin level, with no other source of bleeding on endoscopy. Acute pancreatitis was defined as a three-fold increase in lipase value in the patient's biochemical tests after ERCP. Cholangitis was defined as the occurrence of the Charcot triad (pain, fever, and jaundice).

In patients who did not develop complications during the procedure, those with normal control blood tests (hemogram, amylase) and abdominal examination findings were discharged.

2.2. Follow-up assessment

After the endoscopic removal of CBDS, patients were referred for follow-up 2 weeks later. If stones were present in the gallbladders, laparoscopic cholecystectomy was planned as soon as the gallbladder wall thickness (>3 mm) was normalized in the hepatobiliary ultrasonography. Patients who did not undergo surgery or whose gallbladder wall thickness remained high were called for regular control every 2 months, in which hepatobiliary ultrasonography was performed. When biliary complications were suspected, patients were hospitalized and underwent abdominal computed tomography (to rule out the need for acute surgery) and magnetic resonance cholangiopancreatography (to evaluate the biliary tract). When CBDS recurrence was detected in the follow-up imaging methods in patients whose common bile ducts were completely cleared, it was noted as the first recurrence. ERCP was performed in patients with recurrent CBDS.

2.3. Statistical analysis

All continuous variables are presented as means and standard deviations. Statistical analysis was performed using the Chi-square test for categorical variables and Student *t* test and

Analysis of Variance for continuous variables. Statistical significance was set at $P < .05$. In the determination of recurrent risk factors, logistic regression analysis, a binary logistics method, was used to calculate odds ratios (ORs) with a 95% confidence interval. All data analyses were performed using SPSS statistical software (version 18.0; SPSS Inc., Chicago, IL).

3. Results

3.1. Overall characteristics

A total of 614 patients who underwent their first endoscopic therapy for CBDS were included in this retrospective analysis. The overall mean age was 63.88 (±16.83) years (range: 18–97 years). Three hundred thirty-seven (54.9%) patients were aged 65 years and older. The study included 267 men (43.5%) and 347 women (56.5%). Concomitant diseases were observed in the cardiovascular system in 335 patients (54.6%), kidneys in 477 (12.5%), lung in 153 (24.9%), and central nervous system (CNS) in 60 (9.8%). Nineteen patients (3.1%) had nonperiampullary malignancies. In magnetic resonance cholangiopancreatography, stones were detected in 315 (51.3%) patients, while sludge was observed in 30 (4.9%) patients. EST and needle-knife precut were performed in 506 and 112 (18.2%) patients, respectively. The first and second cannulations were successful in 478 (77.9%) and 137 (22.3%) patients, respectively. The mean common bile duct diameter of the patients was 13.98 (±4.44) mm. During the procedure, stone/sludge was detected in 470 (76.5%) patients, periampullary malignancy in 74 (12.1%) patients, and purulent drainage was observed in the common bile duct in 56 (9.1%) patients. The mean stone diameter was 9.70 (±3.50) mm, and gallbladder stones were detected in 295 (48%) patients. The number of patients who underwent cholecystectomy before the procedure was 174 (28.3%). Nitroglycerin was used in 241 patients (39.3%). Periampullary diverticulum (PAD) was detected in 110 (17.9%) patients, and 8 (1.3%) patients had a T-tube in the common bile duct. A stent was placed in the common bile duct in 136 patients (22.1%). Perioperative bleeding and perforation occurred in 55 (9%) and 5 (0.9%) patients, respectively. Two patients (0.3%) underwent emergency operations. The mean duration of the procedure was 25.21 (±13.355) minutes, ranging between 10 and 60 minutes. Postoperative bleeding and pancreatitis were observed in 2 (0.3%) and 58 (9.4%) patients, respectively. Mortality was observed in 6 (1%). The mean hospital stay was 1.74 (±1.528) days. There was 1 recurrence in 85 patients (13.8%), 2 recurrences in 23 patients (3.7%), and 3 recurrences in 9 patients (1.5%). The mean follow-up duration after the initial treatment of CBDS was 3.3 ± 2.1 years (Table 1).

3.2. Univariate analysis

We examined the factors that increased the recurrence of CBDS in our study using the Chi-square test, Student *t* test, and analysis of variance, and found that 52 (61.2%) female patients did not affect recurrence ($P = .350$), while 73 (85.9%) patients older than 65 years of age did ($P = .000$). With regard to concomitant diseases, 66 (77.6%) patients with cardiovascular diseases ($P = .000$), 37 (43.5%) patients with respiratory diseases ($P = .000$), 17 (20.0%) patients with CNS disease ($P = .001$) had recurrence, while 15 (17.6%) patients with renal disease ($P = .126$), and 4 (4.7%) patients with nonperiampullary malignancies did not ($P = .384$). The common bile duct width was 18.95 (±4.66) mm in the recurrence group ($P = .000$). The mean stone size was 10.36 (±3.99) mm in diameter in the recurrence group, which was not significant for recurrence ($P = .058$).

Table 1

Factors increasing common bile duct stone recurrence using Chi-square, Student *t* test, and ANOVA analyses.

	Recurrence (n = 85) (%)	Nonrecurrence (n = 529) (%)	All (n = 614) (%)	*P*
Sex (female)	52 (61.2)	295 (55.8)	347 (56.5)	.350
Age (>65)	73 (85.9)	264 (49.9)	337 (54.9)	.000
Concomitant diseases				
Cardiovascular	66 (77.6)	269 (50.9)	335 (54.6)	.000
Renal	15 (17.6)	62 (11.7)	77 (12.5)	.126
Lung	37 (43.5)	116 (21.9)	153 (24.9)	.000
CNS	17 (20.0)	43 (8.1)	60 (9.8)	.001
Malignity	4 (4.7)	15 (2.8)	19 (3.1)	.384
CBD diameter	18.95 ± 4.66	13.18 ± 3.84	13.98 ± 4.44	.000
Mean stone size	10.36 ± 3.99	9.59 ± 3.50	9.70 ± 3.50	.058
GB stone	51 (60.0)	244 (46.1)	295 (48.0)	.017
CCX post	32 (37.6)	142 (26.8)	174 (28.3)	.040
Nitroglycerin use	27 (31.8)	214 (40.5)	241 (39.3)	.128
Stent placement	27 (31.8)	109 (20.6)	136 (22.1)	.021
PAD presence	26 (30.6)	84 (15.9)	110 (17.9)	.001
Perioperative purulent drainage	8 (9.4)	48 (9.1)	56 (9.1)	.924
Needle-knife precut	17 (20)	95 (18.0)	112 (18.2)	.651
First cannulation	64 (75.3)	414 (78.3)	478 (77.9)	.541
Second cannulation	21 (24.7)	116 (21.9)	137 (22.3)	.568
Periampullary malignity	13 (15.3)	61 (11.5)	74 (12.1)	.323
Perioperative bleeding	10 (11.8)	45 (8.5)	55 (9.0)	.329
Perioperative perforation	1 (1.2)	4 (0.8)	5 (0.8)	.704
T-tube presence	7 (8.2)	1 (0.2)	8 (1.3)	.000
Operation time	31.44 ± 14.38	24.20 ± 12.92	25.21 ± 13.36	.000

ANOVA = analysis of variance, CBD = common bile duct, CCX = cholecystectomy, CNS = central nervous system, GB = gall bladder, PAD = periampullary diverticulum.

The first cannulation was performed in 64 (75.3%) patients, second cannulation in 21 (24.7%), and needle-knife precut in 17 patients (20.0%), none of which affected recurrence ($P=.541$, $P=.568$, and $P=.651$, respectively). Stones were detected in the gallbladder in 51 (60%) patients before the procedure ($P=.017$). Thirty-two (37.6%) patients underwent cholecystectomy ($P=.040$), both of which were associated with recurrence. Nitroglycerin was used in 27 (31.8%) patients during the procedure ($P=.128$). Purulent drainage was detected in 8 (9.4%) ($P=.651$), and periampullary malignancy was detected in 13 (15.3%) patients ($P=.323$) during the procedure. Ten patients (11.8%) had bleeding, and 1 (1.2%) patient had a perforation ($P=.329$ and $P=.704$, respectively). Stents were used in 27 (31.8%) patients ($P=.021$), PAD was detected in 26 (30.6%) ($P=.001$), and T-tubes were used in 7 (8.2%) patients ($P=.000$), all of which affected recurrence. The procedure time was 31.44 (±14.38) minutes, and prolongation of the procedure affected recurrence ($P=.000$) (Table 1).

3.3. Multivariate analysis

Logistic regression analysis was used to calculate ORs to determine the risk factors for recurrence. Accordingly, female gender (OR 1.250 [0.782–1.997] $P=.351$), concomitant renal (OR 1.088 [0.566–2.092] $P=.801$) or CNS diseases (OR 1.669 [0.867–3.211] $P=.125$), having a periampullary malignancy (OR 1.174 [0.354–3.895] $P=.794$), mean stone size (OR 1.066 [0.998–1.140] $P=.059$), first and second cannulations (OR 0.847 [0.496–1.445], $P=.541$, OR 1.168 [0.685–1.993], $P=.568$, respectively), undergoing a needle-knife precut procedure (OR 1.142 [0.642–2.032] $P=.651$), nitroglycerin use during the procedure (OR 0.685 [0.420–1.117] $P=.129$), purulent drainage (OR 1.039 [0.473–2.281] $P=.924$), bleeding (OR 1.441 [0.696–2.984] $P=.325$), perforation (OR 1.622 [0.179–14.708] $P=.667$), and detection of a periampullary malignancy (OR 1.385 [0.725–2.648] $P=.324$) during the procedure, and PAD (OR 0.957 [0.507–1.805] $P=.891$) were not risk factors for recurrence.

Being older than 65 years (OR 1.084 [1.060–1.109] $P=.000$), concomitant cardiovascular (OR 2.528 [1.418–4.506] $P=.002$) and respiratory diseases (OR 1.766 [1.040–3000] $P=.035$), common bile duct width (OR 1.347 [1.261–1.438] $P=.000$), preoperative GBS (OR 1.752 [1.099–2.793] $P=.018$), stent placement in the common bile duct (OR 1.794 [1.085–2.966] $P=.023$), T-tube use (OR 47,385 [5.752–390,346] $P=.000$), and prolongation of the procedure (OR 1.037 [1.021–1.054] $P=.000$) were risk factors for recurrence, while having undergone cholecystectomy before the procedure (OR 1.645 [1.019–2.657] $P=.042$) reduced the risk (Table 2).

Being over 65 years of age was established as a risk factor for CBDS recurrence. In addition, Kaplan–Meier analysis showed that when follow-up times were considered, the CBDS recurrence rate increased proportionally with age (Table 3, Fig. 1).

There was 1 recurrence in 85 patients (13.8%), 2 recurrences in 23 patients (3.7%), and 3 recurrences in 9 patients (1.5%). Of these 9 patients, 7 had gallstones, the GBS was left in situ, and 2 had undergone cholecystectomy. EST was performed in 3 of the first ampullary interventions, and sphincterotomy was performed using the needle-knife precut method in 6 patients. Perioperative perforation and bleeding related to additional ampullary interventions were seen in 1 and 4 patients, respectively. The patient with perioperative perforation was followed up with a stent placed in the common bile duct, without any need for an emergency operation. Two patients underwent emergency operations, in which the common bile ducts were explored, and T tubes were placed. During common bile duct exploration,

Table 2

Evaluation of common bile duct stone recurrence risk factors using logistic regression analysis.

	Recurrence (n = 85) (%)	Nonrecurrence (n = 529) (%)	OR (95% CI)	P
Sex (female)	52/33	295/234	1.250 (0.782–1.997)	.351
Age (>65)	73/12	264/265	1.084 (1.060–1.109)	.000
Concomitant diseases				
Cardiovascular	66 (77.6)	269 (50.9)	2.528 (1.418–4.506)	.002
Renal	15 (17.6)	62 (11.7)	1.088 (0.566–2.092)	.801
Lung	37 (43.5)	116 (21.9)	1.766 (1.040–3.000)	.035
CNS	17 (20.0)	43 (8.1)	1.669 (0.867–3.211)	.125
Malignity	4 (4.7)	15 (2.8)	1.174 (0.354–3.895)	.794
CBD diameter	18.95 ± 4.66	13.18 ± 3.84	1.347 (1.261–1.438)	.000
Mean stone size	10.36 ± 3.99	9.59 ± 3.50	1.066 (0.998–1.140)	.059
GB stone	51 (60.0)	244 (46.1)	1.752 (1.099–2.793)	.018
CCX post	32 (37.6)	142 (26.8)	1.645 (1.019–2.657)	.042
Nitroglycerin use	27 (31.8)	214 (40.5)	0.685 (0.420–1.117)	.129
Stent placement	27 (31.8)	109 (20.6)	1.794 (1.085–2.966)	.023
PAD presence	26 (30.6)	84 (15.9)	0.957 (0.507–1.805)	.891
Perioperative purulent drainage	8 (9.4)	48 (9.1)	1.039 (0.473–2.281)	.924
Needle-knife precut	17 (20)	95 (18.0)	1.142 (0.642–2.032)	.651
First cannulation	64 (75.3)	414 (78.3)	0.847 (0.496–1.445)	.541
Second cannulation	21 (24.7)	116 (21.9)	1.168 (0.685–1.993)	0.568
Periampullary malignity	13 (15.3)	61 (11.5)	1.385 (0.725–2.648)	.324
Perioperative bleeding	10 (11.8)	45 (8.5)	1.441 (0.696–2.984)	.325
Perioperative perforation	1 (1.2)	4 (0.8)	1.622 (0.179–14.708)	.667
T-tube presence	7 (8.2)	1 (0.2)	47.385 (5.752–390.346)	.000
Operation time	31.44 ± 14.38	24.20 ± 12.92	1.037 (1.021–1.054)	.000

95% CI = 95% confidence interval, CBD = common bile duct, CCX = cholecystectomy, CNS = central nervous system, GB = gall bladder, OR = odds ratio, PAD = periampullary diverticulum.

Table 3

Evaluation of CBDS recurrence times by age groups in the 5-years follow-up period.

Recurrence time				Years				
				<50 yr	51–60 yr	61–70 yr	>70 yr	Total
1.00	Recurrence1	1.00	Count				3	3
			% of total	–	–	–	100.0%	100.0%
	Total		Count				3	3
			% of total	–	–	–	100.0%	100.0%
2.00	Recurrence1	1.00	Count			1	4	5
			% of total	–	–	20.0%	80.0%	100.0%
	Total		Count			1	4	5
			% of total	–	–	20.0%	80.0%	100.0%
3.00	Recurrence1	1.00	Count			4	11	15
			% of total	–	–	26.7%	73.3%	100.0%
	Total		Count			4	11	15
			% of total	–	–	26.7%	73.3%	100.0%
4.00	Recurrence1	1.00	Count		2	5	20	27
			% of total	–	7.4%	18.5%	74.1%	100.0%
	Total		Count		2	5	20	27
			% of total	–	7.4%	18.5%	74.1%	100.0%
5.00	Recurrence1	1.00	Count	3	5	1	26	35
			% of total	8.6%	14.3%	2.9%	74.3%	100.0%
	Total		Count	3	5	1	26	35
			% of total	8.6%	14.3%	2.9%	74.3%	100.0%

CBDS = common bile duct stones.

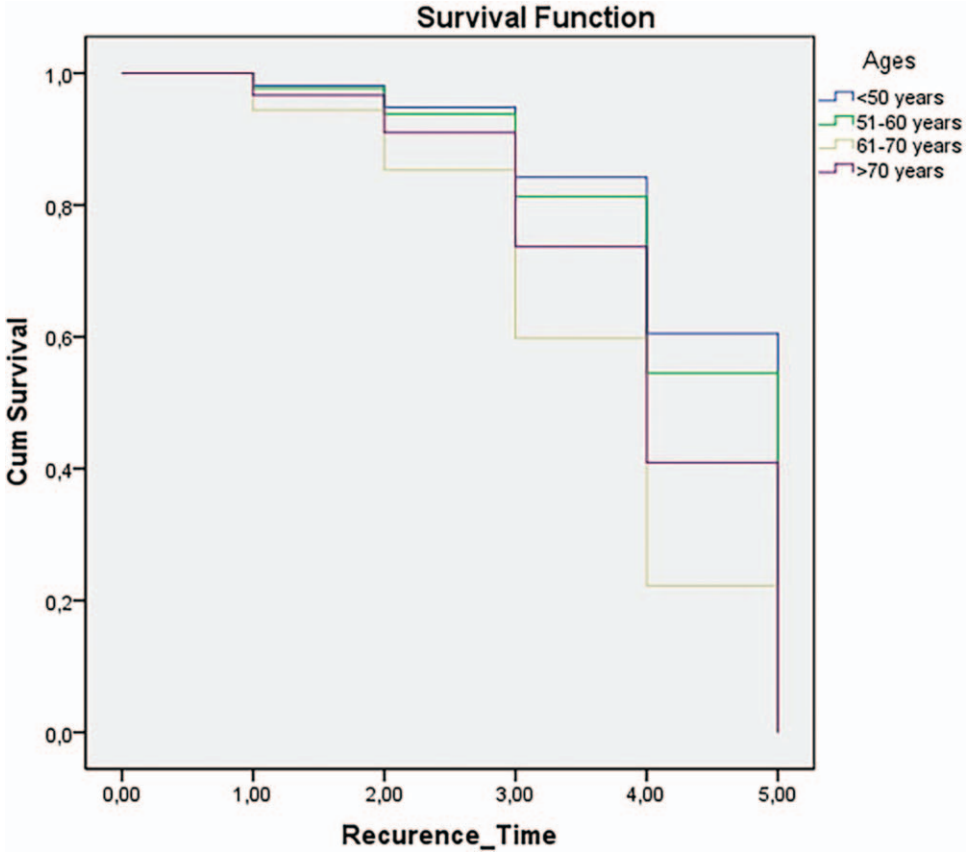

Figure 1. Evaluation of CBDS recurrence with age in Kaplan–Meier analysis. CBDS = common bile duct stones.

stones were seen filling the CBD until the intrahepatic ducts. A periampullary malignancy was detected in another operation, and hepaticojejunostomy was performed. Mortality was observed in 6 patients. Four of these patients had cardiovascular or respiratory diseases and died during follow-up. One of the other 2 patients died during the operation because of respiratory failure, and 1 died due to septic shock and multi-organ failure during the postoperative follow-up.

4. Discussion

Studies have reported the recurrence rate of CBDS after ERCP between 2% and 22%.[8] In our study, once CBDS recurred, the rate of next recurrence increased in proportion to the number of recurrence cases, as previously reported.[9] Varying risk factors have been reported in studies.[1–8] In our study, age (>65 years), presence of concomitant cardiovascular and respiratory diseases, stent or T-tube placement in the common bile duct, a previously known wide common bile duct (diameter ≥ 10 mm), and gallbladder stones were independent risk factors.

The recurrence rate of choledocholithiasis in elderly patients (>65 years) may be as high as 30%.[10] The specific mechanism is not clear, but Akaydın et al[11] suggested that secondary risk factors such as common bile duct dilation and especially PAD, which cause retrograde infection in the papilla, increase the risk of CBDS; this risk is higher in the papillae located within the diverticula. PAD is rare in patients under 40 years of age, and its incidence increases with age. Similarly, in our study, CBDS recurrences were more common among elderly patients, advanced age (>65 years) was an independent factor for recurrent CBDS, and a second or more recurrences may develop due to papillary sphincter insufficiency and the presence of PAD with increasing age. However, PAD was detected in 26 (30.6%) of our patients, and although it was found to affect recurrence ($P = .001$), unlike other studies, PAD was not a risk factor (OR 0.957 [0.507–1.805] $P = .891$).

Surgical removal of CBDS, whether open or laparoscopic, is rarely performed and is usually preferred in patients in whom ERCP fails.[12] Exploration of the common bile duct should be considered in patients with hard, large, and multiple stones in whom ERCP fails. The currently used method is laparoscopic exploration. Open exploration and T-tube drainage, both of which were commonly used in the past, are independent risk factors for CBD stenosis and recurrent CBDS. Choledocholithotomy, which causes necrosis and scarring in the epithelial cells of the biliary tract, results in biliary tract stenosis and biliary excretion disorders.[13,14] In the current study, stenting (OR 1.794, $P = .023$) or T-tube placement in the common bile duct (OR 47.385, $P = .000$) appeared to be risk factors for recurrence.

EST, needle-knife precut sphincterotomy, multiple ERCP procedures, and intraoperative ERCP surgeries can cause sphincter dysfunction in Oddi. Intestinal fluid reflux occurs due to sphincter failure, which leads to bile duct infection, thus promoting stone recurrence.[15] Since bacterial contamination of the bile duct is a common finding in patients with choledocholithiasis, prophylactic antibiotics were administered in all procedures, and treatment was continued when necessary.

Nitroglycerin was administered to relax the sphincter smooth muscles. Our selective cannulation rate was high in patients treated with nitroglycerin, which resulted in a decrease in complication rates resulting from precut sphincterotomy.[16] However, no decrease was found in the number of relapsed CBDS in patients administered nitroglycerin, which suggests that nitroglycerin administration may reduce the incidence of complications but does not prevent recurrent CBDS eventually.

The risk of recurrent CBDS was increased in common bile duct stents that were not removed for a long time, and the risk of migration increased in stents that remained for more than 2 months. This causes bile salt accumulation due to their adhesion to the stents. Placing a bile duct stent may affect bile duct dynamics and predispose the patient to cholestasis. Bile concentration can induce inflammatory changes in the common bile duct mucosa, causing the precipitation of inflammatory cells that promote stone recurrence.[17] In our clinical practice, we keep the stents for a maximum of 2 months, and we arrange ursodeoxycholic acid treatment for each patient who has a stent.

Large stones cause further dilation of the bile ducts and impair their function, leading to difficulties in bile excretion, which can easily cause cholestasis and bacterial infections.[18] In our study, unlike other studies, mean stone size did not affect recurrence, and it was not a risk factor (OR 1.066 [0.998–1.140], $P = .059$). In this regard, we performed surgical intervention in our clinic for large stones. Lithotripsy is a treatment option; however, it is not used in our clinic.

While risk factors for CBDS recurrence have been extensively studied, risk factors for multiple CBDS recurrences have not been fully elucidated. In our study, unoperated GBS, advanced age (>65 years), T-tube placement, and common bile duct stents in place for more than 2 months were independent risk factors for multiple recurrences. Concomitant diseases were also evaluated, unlike other studies, and respiratory/cardiovascular diseases were independent risk factors.

Although patients' clinical data were extensively analyzed and risk factors for recurrence of CBDS after ERCP were thoroughly investigated, this retrospective study still had limitations. First, this was a retrospective study performed at a single institution. While EST is the current standard of care, it was the first ampullary intervention in 18.2% of our needle-knife precut sphincterotomy cohort. The incidence and causes of recurrent CBDS may differ between patients with EPBD and EST. A randomized controlled study reported preservation of the sphincter of Oddi in 17% of cases after EST and 8% of those after EPBD.[19,20] EPBD was not performed in the current study, which may have caused bias. Second, we did not analyze the stone composition and were unable to distinguish CBDS recurrence. Third, the diagnostic yield of CBDS was altered due to improved imaging modality over the long study period, which may have caused a bias in the CBDS recurrence rate.

5. Conclusion

CBDS recurrence and multiple recurrences, especially in those with multiple stones during the first recurrence, are not rare after endoscopic interventions. Although we may alter some factors, such as gallstones, nonlaparoscopic exploration, prolonged stent stay-in, and T-tube placement, some factors (>65 years of age and having cardiovascular or respiratory diseases) are non-alterable. After the first recurrence of CBDS, the probability of multiple recurrences increases depending on multiple factors.

Author contributions

The first draft of the manuscript was written by Tamer AKAY, and all the authors commented on the previous versions of the manuscript. All authors read and approved the final manuscript.

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