Long- and short-term outcomes of ERCP for bile duct stones in patients over 80 years old compared to younger patients: a propensity score analysis

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Backgrounds and study aims: Endoscopic sphincterotomy (ES) is widely accepted as first-line therapy for bile duct stones (BDS). The major long-term pancreaticobiliary complication is BDS recurrence. Whether cholecystectomy should be performed after ES, especially in elderly patients, remains controversial. The aim of this study is to investigate the short-term and long-term outcomes after therapeutic endoscopic retrograde cholangiopancreatography (ERCP) for BDS and to analyze risk factors for pancreaticobiliary complications. We also compared long-term outcomes in patients older and younger than age 80.
Patients and methods: A total of 1210 patients who underwent therapeutic ERCP for BDS were retrospectively reviewed to identify risk factors for pancreaticobiliary complications. We divided these patients into two groups: Group Y (<80 years; 960 patients) and Group O (≥80 years; 250 patients). There were 192 matched pairs in the propensity score analysis.
Results: The incidence of pancreaticobiliary complications was 13.1% (126/960) in Group Y and 20.4% (51/250) in Group O ($P<0.00001$). Multivariate analysis showed that a gallbladder left in situ with stones was a significant independent risk factor (hazard ratio, 2.81; 95% confidence interval, 1.62–4,89; $P=0.0002$). There were no significant differences in the incidence of pancreaticobiliary complications between the propensity score-matched groups.
Conclusions: A gallbladder in situ with stones was the only significant risk factor for pancreaticobiliary complications after treatment for BDS. Age per se should not be the major factor when deciding on treatment that minimizes the occurrence of pancreaticobiliary disease.

Introduction

Bile duct stones (BDS) are a common pancreaticobiliary disease for which early diagnosis and emergency treatment are necessary. Once the complication of acute obstructive suppurative cholangitis develops, it often becomes fatal, especially in elderly patients. To prevent such complications, therapeutic ERCP is performed. Endoscopic sphincterotomy (ES) is widely accepted as first-line therapy for BDS [1]. After treatment for BDS, the major long-term pancreaticobiliary complication is BDS recurrence.

Several studies have investigated the long-term outcomes of ES [2–6]. A few studies have reported that leaving the gallbladder in situ is a risk factor for pancreaticobiliary complications [3,6]. Consequently, cholecystectomy is performed at many institutions after ES, but it is thought to be a risk factor for BDS, due to decreased sphincter of Oddi function and increases in the number and size of periampullary diverticula [7]. A decision about whether to perform cholecystectomy must also depend on the operative risk to the patient. Whether cholecystectomy should be performed after ES remains controversial, especially in elderly patients who tend to have comorbidities. In this study, our primary objective was to investigate the short-term and long-term outcomes after therapeutic ERCP for BDS, and to analyze risk factors for pancreaticobiliary complications. We also compared long-term outcomes between two groups: patients older and younger than age 80 years. Because the validity of treatment effects in observational studies may be limited by selection bias and confounding factors, we performed the analysis using a propensity score approach.

Patients and methods

Patients

Between September 1982 and April 2011, 1389 patients with BDS underwent therapeutic ERCP

at our institution and BDS extraction was successful in 1358 of them. Reliable follow-up information was available for 1210 of the patients, who we divided into two groups: Group Y (age < 80 years) and Group O (age ≥ 80 years).

Procedures

Written informed consent was obtained for therapeutic ERCP and follow-up examination. We preferred to perform EPBD in the following situations: (a) maximum diameter of the largest stone less than 10 mm, (b) three or fewer stones, (c) patient age less than 50 years, or (d) presence of comorbid disease. ES or endoscopic papillary balloon dilation (EPBD) was performed by experienced endoscopists with intravenous sedation. Except in patients with symptoms of acute cholangitis, we did not use prophylactic antibiotics after therapeutic ERCP. ES was performed after deep cannulation of the BD with a "long-nose" papillotome, or in more recent years, a short-nose papillotome inserted over a guidewire, followed by an incision over the roof of the ampulla. Standard techniques were used to remove BDS. A balloon, four-wire basket catheter, or both were used for stone extraction. Patients with large stones underwent mechanical lithotripsy. Mechanical lithotripsy was used to crush stones larger than 10 mm in diameter. Balloon-occlusion cholangiography was performed at the end of stone extraction. The common bile duct and intrahepatic ducts were carefully examined to exclude the presence of residual calculi. No cases were conducted with lithotripsy under cholangioscopic control. If necessary, we performed intraductal ultrasonography. Treatment was repeated until confirmation that all stones were extracted.

Post-ERCP complications were defined according to the 1991 consensus guidelines [8]. Procedure-induced pancreatitis was defined as the onset of new abdominal pain with at least a three-fold elevation in serum amylase more than 24 hours after the procedure. Hemorrhage was defined as clinical evidence of bleeding with a decrease in hemoglobin greater than 2 g/dL and the need for endoscopic treatment or interventional radiology. Cholangitis was defined as an elevation in temperature to more than 38 °C that was thought to have a biliary cause, without evidence of other concomitant infections. Cardiovascular and pulmonary disease at the time of the procedure or within 30 days included ischemic disease, congestive heart failure, significant cardiac arrhythmia requiring treatment, aspiration, and hospital-acquired pneumonitis. Perforation included retroperitoneal or bowel-wall perforation visualized using any imaging modality.

Follow-up data were collected by phone calls or personal interviews if the patient was not seen for follow-up at the hospital for more than 1 year. During follow-up, all patients underwent abdominal ultrasound and liver function testing every 6 months. Patients who skipped hospital visits for more than 1 year were asked about the recurrence of pancreaticobiliary complications and further interventional procedures. Follow-up research was completed in August 2014.

Statistical analysis

Continuous variables are expressed as means and standard deviation (SD). Continuous variables were compared using Student's *t*-test or the Wilcoxon rank-sum test, as appropriate. Categorical variables were tested using the chi-square test with Yate's correction or Fisher's exact test for small expected frequencies. Actuarial analysis of the cumulative incidence of pancreaticobiliary disease was estimated using the Kaplan-Meier method and differences was tested using the log-rank test. Potential risk factors for pancreaticobiliary disease were initially assessed with univariate analysis. Predictive risk factors for pancreaticobiliary disease that had a *P* value < 0.05 in the univariate and multivariate analysis were included in a Cox proportional hazards model, and hazards ratios and 95 % confidence intervals (95 % CIs) were calculated.

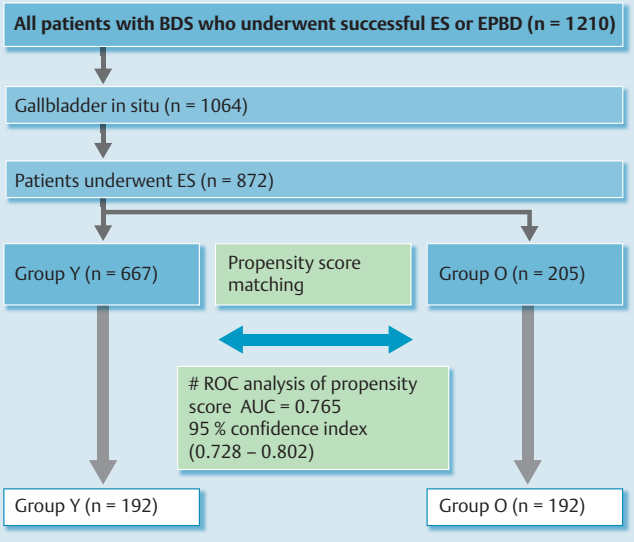


Fig. 1 Flowchart of the patient selection process. Group Y: age < 80 year; 960 patients. Group O: age ≥ 80 years; 250 patients

Of the 1210 study patients, 136 had a history of previous cholecystectomy. The remaining 1064 patients had gallbladders in situ. Of the 872 patients treated with ES, there were 667 patients in Group Y and 205 patients in Group O (**Fig. 1**). Propensity scores were estimated using a multiple logistic regression model for the 872 patients. Forward stepwise selection was used to select variables for the regression model. Sex, bile duct diameter, diameter of the largest stone, presence of periampullary diverticula, and Gallbladder status were adjusted in propensity score matching. We considered *P* values less than 0.05 to be statistically significant. Statistical analysis was performed with SPSS, version 18.0 for Windows (IBM, Tokyo, Japan).

Results

Patient characteristics

During the study period, therapeutic ERCP had a success rate of 97.8 % (1358/1389). We were able to obtain reliable follow-up data for more than 6 months in 1210 patients, consisting of 657 men and 553 women, with a mean age of 67.3 ± 14.8 years (range, 18 – 98). Treatment consisted of one of two procedures: 956 patients underwent ES and 254 patients underwent endoscopic papillary balloon dilatation (EPBD).There were 250 patients who were age 80 or older (Group O) and 960 patients who were younger than age 80 (Group Y). Patient characteristics for the two groups are shown in **Table 1**. Group O had a significantly higher proportion of female patients than did Group Y. In Group O, maximum stone diameter and bile duct diameter were significantly larger (**Fig. 2** and **Fig. 3**). In Group Y, 11.8 % (113/960) of the patients had a history of cholecystectomy, compared to 13.2 % (33/250) of the patients in Group O. The proportion of patients with gallbladders in situ with stones was 70.6 % (678/960)

	Group Y (n = 960)	Group O (n = 250)	*P* value
Age (years)[1]	62.8 ± 12.9 (18 – 79)	85.1 ± 4.2 (80 – 98)	0.0011
Sex (male/female)	539/421	118/132	< 0.0001
Diameter of the largest stone (mm)[1]	8.2 ± 5.7 (1 – 40)	10.5 ± 6.2 (1 – 30)	< 0.0001
Diameter of the bile duct (mm)[1]	12.1 ± 4.3 (3 – 30)	14.3 ± 0.5 (4 – 35)	0.0029
Number of stones: 1	580 (60.4 %)	125 (50.0 %)	
Number of stones: ≥ 2	380 (39.6 %)	125 (50.0 %)	
Periampullary diverticula	255 (26.6 %)	124 (49.6 %)	< 0.0001
Single stone with a diameter < 10 mm	450 (46.9 %)	66 (26.4 %)	< 0.0001
ES	720 (75.0 %)	236 (94.4 %)	< 0.0001
Previous cholecystectomy	113 (11.8 %)	33 (13.2 %)	NS
Gallbladder in situ with stones	678 (70.6 %)	164 (65.6 %)	NS
Gallbladder in situ without stones	169 (17.6 %)	53 (21.2 %)	NS

ES, endoscopic sphincterotomy
NS, Not significant
[1] Values are expressed as means ± SD (range)

Table 1 Baseline characteristics of the study patients.

in Group Y and 65.6 % (164/250) in Group O. The proportion of patients with gallbladders in situ without stones was 17.6 % (169/960) in Group Y and 21.2 % (53/250) in Group O. There was no significant difference between the two groups with regard to the status of the gallbladder before endoscopic treatment. The proportion of patients who underwent cholecystectomy after endoscopic treatment was significantly higher in Group Y than in Group O (49.9 % [479/960] versus 13.2 % [33/250], $P < 0.00001$). The procedure used to treat BDS depended on the size and number of stones and the condition of the bile duct. Consequently, the proportion of patients who underwent EPBD was lower in Group O than in Group Y (**Fig. 4**).

Immediate complications

Immediate complications occurred in 6.5 % of patients (79/1210). Complications by group are shown in **Table 2**. Post-ERCP pancreatitis developed in 22 patients in Group Y and five patients in Group O. Hemorrhage occurred in 23 patients in Group Y and five patients in Group O. Severe hemorrhage after ES occurred in an 85-year-old man. Despite multiple epinephrine injections and blood transfusions over several days, he required treatment by interventional radiology, which was successful [9]. He fully recovered and was discharged from the hospital without any further complications.

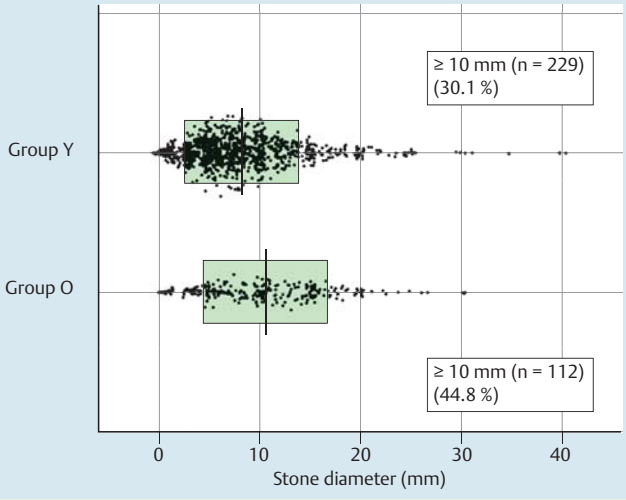


Fig. 2 Diameter of the largest stone in the two groups. The diameter of the largest stone was significantly larger in Group O than in Group Y ($P < 0.0001$).

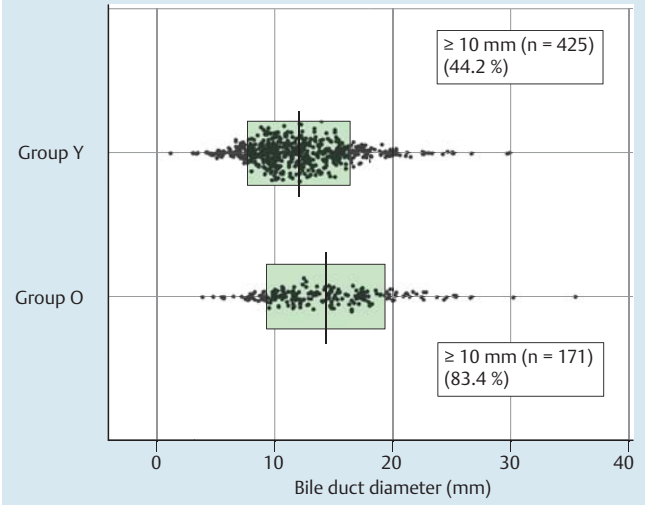


Fig. 3 Bile duct diameter in the two groups. Group O had a significantly larger mean bile duct diameter than Group Y ($P < 0.0001$).

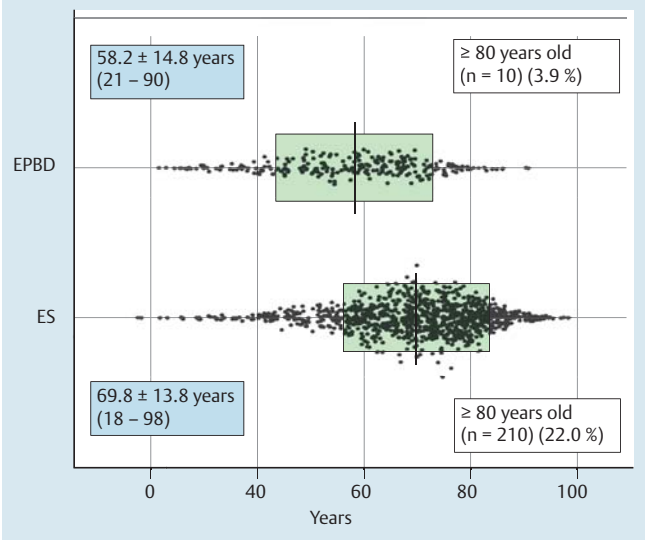


Fig. 4 The EPBD group included 10 (3.9 %) patients aged ≥ 80 years. The ES group included 210 (22.0 %) patients aged ≥ 80 years.

Group Y (n = 960)	Group O (n = 250)	P value
Acute pancreatitis[1]	2.3 % (23/960)	2.0 % (5/250)	NS
Hemorrhage	2.3 % (23/960)[2]	2.0 % (5/250)	NS
Acute cholangitis	0.7 % (7/960)	1.6 % (4/250)	NS
Acute cholecystitis	0.2 % (2/960)	0 % (0/250)	NS
Cardiovascular or pulmonary disease	0.4 % (3/960)	2.0 % (5/250)	0.0117
Gastrointestinal tract perforation	0.2 % (2/960)	0.4 % (1/250)	NS
Total	6.2 % (60/960)	7.6 % (19/250)	

NS, non-significant
[1] Defined using Cotton's criteria
[2] One patient with liver cirrhosis died of liver failure due to hemorrhage.

Table 2 Immediate complications (< 30 days).

Group Y (n = 960)	Group O (n = 250)
Mean duration of follow-up, days (range)	2637.3 ± 1999.7(189 – 11628)	1278 ± 956.2 (184 – 5867)
Incidence rate	13.1 % (126/960)	20.4 % (51/250)
Mean time to incident , days (range)	860.4 ± 648.3(183 – 5862)	464.3 ± 225.6 (197 – 1655)
Bile duct stone recurrence	10 % (96/960)	14.8 % (37/250)
Acute cholangitis	2.4 % (23/960)	3.6 % (9/250)
Acute cholecystitis	0.7 % (7/960)	1.6 % (4/250)
Acute pancreatitis	0.4 % (4/960)	1.6 % (4/250)
Biliary malignancies	0.2 % (2/960)	0 % (0/250)
Total	132[1]	54[1]

[1] Includes overlapping cases.

Table 3 Incidence of pancreaticobiliary complications.

Early mortality due to ERCP-related complications occurred in two Group Y patients. A 55-year-old man with Child-Pugh C cirrhosis died of liver failure due to hemorrhage after EPBD. A 62-year-old man died of severe necrotizing pancreatitis after ES.
The frequency of cardiovascular and pulmonary diseases was significantly higher in Group O than in Group Y. Cardiovascular and pulmonary diseases in Group Y included one patient with each of the following: severe heart failure, aspiration pneumonia, and arrhythmia. All of them required treatment. In contrast, cardiovascular and pulmonary diseases in Group O consisted of severe heart failure in two patients, aspiration pneumonia in two patients, and coronary heart disease in one patient (**Table 2**).

Long-term outcomes

We were able to gather long-term data on 1210 of 1358 patients successfully treated with therapeutic ERCP (89.1 %), with a mean follow-up of 2637.3 ± 1999.7 days (range, 189 – 11628 days) in Group Y and 1278.0 ± 956.2 days (range, 184 – 5867 days) in Group O ($P < 0.00001$). The incidence of pancreaticobiliary complications was 13.1 % (126/960 patients) in Group Y and 20.4 % (51/250 patients) in Group O. The mean time to an incident was 860.4 ± 648.3 days (range, 183 – 5862 days) in Group Y and 464.3 ± 225.6 days (range, 197 – 1655 days) in Group O. The difference in the time to a pancreaticobiliary complication between the two groups was significant ($P < 0.00001$). The most common pancreaticobiliary complication was BDS recurrence, which occurred in 10 % (96/960) of Group Y and 14.8 % (37/250) of Group O. For recurrent BDS, the rate of successful endoscopic stone removal was 97.0 % (129/137). Two patients required surgery for BDS removal, and two patients underwent endoscopic biliary stent placement.
Multiple episodes of stone recurrence were observed in 0.8 % (10/1210) of patients. The median number of multiple stone recurrences was 3 (range, 2 – 6). Two recurrences developed in four patients and three or more recurrences developed in six patients. There was no significant difference between Groups Y and O in the proportion of patients with multiple recurrences (0.7 % [7/960] versus 1.2 % [3/250]). Other complications in Groups Y and O (34 and 17 cases, respectively) included acute cholangitis, 2.4 % (23/960) and 3.6 % (9/250); acute cholecystitis, 0.7 % (7/960) and 1.6 % (4/250); and acute pancreatitis, 0.4 % (4/960) and 1.6 % (4/250), respectively (**Table 3**).
During the follow-up period, biliary malignancy was diagnosed in two patients. One patient in Group Y was diagnosed with bile duct carcinoma 8.9 years after undergoing ES.The other patient, also in Group Y, was diagnosed with bile duct carcinoma 10.9 years after EPBD.
Based on Kaplan-Meier analysis, there was a lower incidence of pancreaticobiliary complications in Group Y than in Group O. The cumulative recurrence rates at 2 and 3 years were 8.1 % and 10.8 %, respectively, in Group Y versus 21.3 % and 27.3 %, respectively, in Group O (**Fig. 5**) (log-rank test, $P < 0.00001$).
Prognostic factors for pancreaticobiliary complications. The results of the univariate and multivariate analysis of pancreaticobiliary complications are shown in **Table 4** and **Table 5**. Age, sex (female), treatment (ES), stone size, bile duct diameter, and the presence of a gallbladder in situ were identified as risk factors for pancreaticobiliary complications. Based on the state of the treated gallbladder, we divided the patients into four groups as follows: (A) cholecystectomy (CCx) after therapeutic ERCP; (B) history of prior cholecystectomy; (C) gallbladder left in situ without stone; and (D) gallbladder left in situ with stones (**Table 4**).
We used Cox proportional hazards model to analyze risk factors for pancreaticobiliary complications. Multivariate analysis for pancreaticobiliary complications showed that a gallbladder left in situ with stones was a significant independent risk factor (hazard ratio, 3.91; 95 % CI, 2.20 – 6.93, $P < 0.00001$) (**Table 5**).
Kaplan-Meier analysis showed a significantly lower incidence of pancreaticobiliary complications in the group who underwent CCx after therapeutic ERCP compared to the group with a gallbladder left in situ with stones (**Fig. 6**).

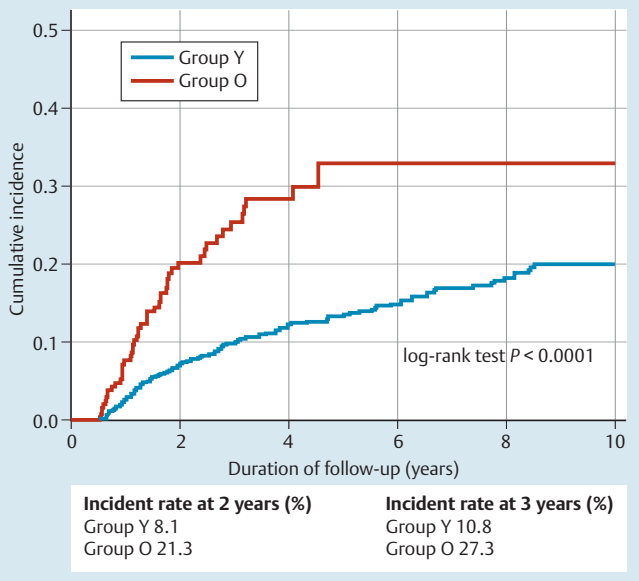


Fig. 5 Kaplan-Meier curves showing the cumulative incidence of pancreaticobiliary complications in patients by age group ($P<0.0001$).

Propensity score analysis

There were 192 pairs of matched patients (**Fig. 1**). One-to-one matching was performed using the greedy matching method. Goodness of fit was evaluated using Hosmer-Lemeshow statistics ($\chi^2=2.838$, $df=6$, $P=0.829$). The area under the curve (AUC) with receiver operating characteristic (ROC) analysis for the propensity score was 0.765 (95 % CI, 0.728 – 0.802).The baseline characteristics of the 192 propensity-score matched pairs are summarized in **Table 6**. There were no significant differences in sex, bile duct diameter, largest stone diameter, presence of periampullary diverticula, and gallbladder status (**Table 6**). Kaplan-Meier analysis did not show significant differences in the incidence of pancreaticobiliary complications between the two propensity score-matched groups (log-rank test $P=0.7310$) (**Fig. 7**).

Discussion

ERCP is a widely used first-line treatment for BDS. Due to diminished sphincter of Oddi function and increases in the number and size of periampullary diverticula [7], BDS occurs more frequently in elderly individuals. The number of octogenarians and patients who undergo ERCP is increasing as a result of the aging of society in developed countries [10]. There are some reports comparing endoscopic treatment to laparoscopic cholecystectomy for BDS [11,12]. Since laparoscopic cholecystectomy (LC) has become

Table 4 Univariate analysis of risk factors for pancreaticobiliary complications.

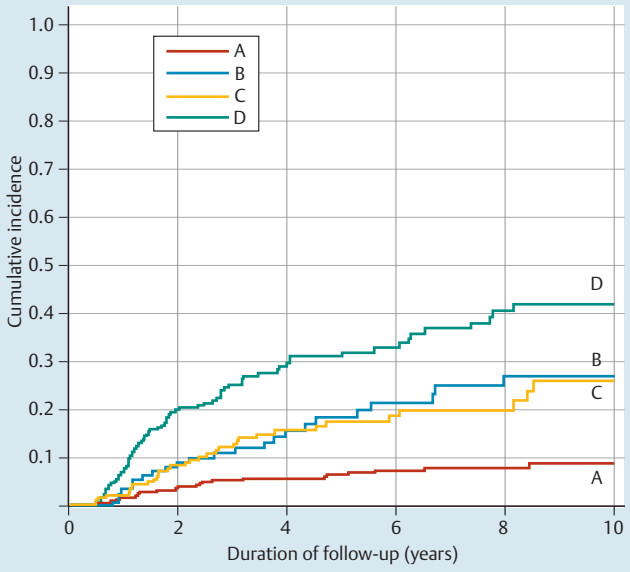
Category	Hazard ratio (95 % confidence interval)		P value
Age (years)		1.03471 (1.0218 – 1.0477)	0.0022
Sex	Male	1	
	Female	1.5559 (1.1562 – 2.0937)	0.0035
Treatment	EPBD	1	
	ES	1.7533 (1.1687 – 2.630)	0.0066
Diameter of the largest stone (mm)		1.02991 (1.0077 – 1.0525)	0.0079
Bile duct diameter (mm)		1.08631 (1.0185 – 1.1204)	0.0065
Gallbladder status	Cholecystectomy after therapeutic ERCP	1	
	History of cholecystectomy	2.8055 (1.6495 – 4.7715)	0.0014
	Gallbladder left in situ without stones	2.7616 (1.7004 – 4.4850)	0.0004
	Gallbladder left in situ with stones	5.5895 (3.6850 – 8.4785)	0.0000
Periampullary diverticula	Present	1	
	Absent	1.1132 (0.8276 – 1.5516)	0.4352

ERCP, endoscopic retrograde cholangiopancreatography. EPBD, endoscopic papillary balloon dilatation. ES, endoscopic sphincterotomy.

Table 5 Multivariate analysis of risk factors for pancreaticobiliary complications.

Category	Hazard ratio (95 % confidence interval)		P value
Age (years)		1.0162 (0.9971 – 1.0356)	0.0956
Sex	Male	1	
	Female	1.4347 (0.9556 – 2.1540)	0.0816
Treatment	EPBD	1	
	ES	1.3509 (0.7331 – 2.489)	0.3347
Diameter of the largest stone (mm)		0.9946 (0.9569 – 1.0338)	0.7855
Bile duct diameter (mm)		1.1763 (0.7188 – 1.9438)	0.5262
Gallbladder status	Cholecystectomy after therapeutic ERCP	1	
	History of cholecystectomy	1.6660 (0.8027 – 3.4577)	0.1706
	Gallbladder left in situ without stones	1.4713 (0.7767 – 2.7869)	0.2360
	Gallbladder left in situ with stones	2.8130 (1.6184 – 4.8894)	0.0002
Periampullary diverticula	Present	1	
	Absent	0.7078 (0.4590 – 1.0914)	0.1178

ERCP, endoscopic retrograde cholangiopancreatography



Incident rate at 3 years (%)		Incident rate at 5 years (%)	
Group A	3.4	Group A	4.7
Group B	8.2	Group B	18.7
Group C	12.4	Group C	15.1
Group D	21.7	Group D	27.4

Fig. 6 Kaplan-Meier curves showing the cumulative incidence of pancreaticobiliary complications in patients by gallbladder status (Group A versus Group D; $P<0.0001$). A: Cholecystectomy after therapeutic ERCP. B: History of cholecystectomy. C: Gallbladder left in situ without stones. D: Gallbladder left in situ with stones.

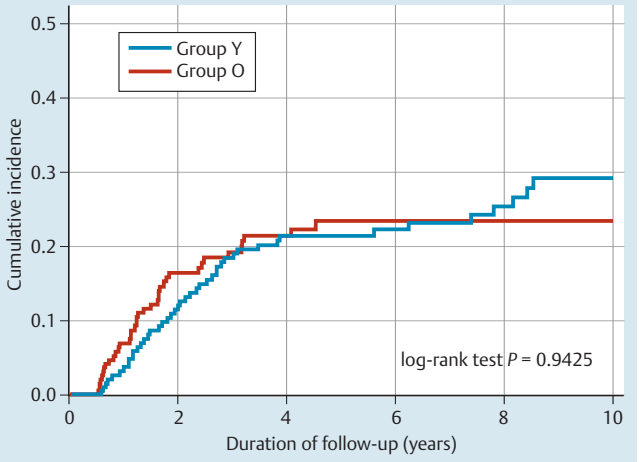


Fig. 7 Kaplan-Meier curves showing the cumulative incidence of pancreaticobiliary complications in propensity score-matched patients classified by age group ($P=0.9425$).

widely adapted, it has become more common in patients aged 80 and older [13]. Therapeutic ERCP and LC currently are used to treat BDS in elderly patients with gallstones but there have been relatively few reports on therapeutic ERCP in the elderly [10].

ES has become accepted as a standard technique for treatment of BDS since it was first used more than 40 years ago [14]. With the advent of LC, EPBD, first reported in 1983 [15], was expected to become another treatment option. However, EPBD is not a commonly used method worldwide for the treatment of BDS because of the high incidence of post-procedure pancreatitis. Currently, EPBD is mainly performed in Japan. Only a few studies have been published [16, 17], although several have reported on long-term outcomes of ES [2–6]. Because sphincter of Oddi function is preserved in EPBD [18], multiple sessions may be required for patients with large stones. Preservation of papillary function decreases the degree of bacteriocholia and the incidence of reflex cholangitis [19].

ES and EPBD each has a characteristic profile of immediate complications; acute pancreatitis is more common with EPBD

Table 6 Characteristics of the two propensity score – matched groups.

	Group Y (n = 192)	Group O (n = 192)	P value
Sex (male/female)	88/104	88/104	NS
Bile duct diameter (mm): mean ± SD (range)	12.1 ± 3.6 (3 – 27)	13.3 ± 3.7 (4 – 27)	NS
Diameter of the largest stone (mm): mean ± SD(range)	10.4 ± 6.5 (2 – 40)	10.4 ± 5.8 (2 – 30)	NS
Periampullary diverticula (present/absent)	83/109	86/106	NS
Gallbladder status			
(A) Cholecystectomy after therapeutic ERCP	32	32	NS
(B) Gallbladder left in situ without stones	49	49	NS
(C) Gallbladder left in situ with stones	111	111	NS
	192	192	

ERCP, endoscopic retrograde cholangiopancreatography; NS, non-significant

Table 7 Incidence of pancreaticobiliary complications.

Recurrence rate (%)			
Gallbladder status	ES (n = 956)	EPBD (n = 254)	Total (n = 1210)
A	7.0 % (26/371)	2.8 % (4/141)	5.8 % (30/512)
B	17.0 % (21/124)	18.2 % (4/22)	17.1 % (25/146)
C	16.1 % (29/180)	16.6 % (7/42)	16.2 % (36/222)
D	26.0 % (73/281)	26.5 % (13/49)	26.1 % (86/330)
	15.9 % (152/956)	9.8 % (25/254)	14.6 % (177/1210)

ES, endoscopic sphincterotomy; EPBD, endoscopic papillary balloon dilation

whereas biliary infection and hemorrhage occur are more frequent with ES [20]. However, we observed one mortality for hemorrhage after EPBD in the present study in a patient with Child-Pugh C cirrhosis. He died of liver failure 22 days after the hemorrhage was controlled with endoscopic management. Our case occurred during stone extraction, although EPBD was performed safely.

Treatment of BDS in patients with cirrhosis should be performed carefully, even if it consists of EPBD. In **Fig. 1**, weshowed that the diameter of the largest stone was significantly larger in Group O than in Group Y. Nearly half of Group O patients had large stones (510/960). Therefore, in the current study, we performed ES on 94.4% of patients (236/254) in Group O and 75.0% (720/956) of patients in Group Y. It is generally difficult to predict differences in long-term complications in ES versus EPBD because we chose the procedure based on the diameter of the bile duct, the size and number of stones, and other patient factors. For both methods, the most common pancreaticobiliary complication is the recurrence of BDS. In a large, multicenter, randomized controlled study, Yasuda et al found that the incidence of biliary complications was significantly higher in the ES group than in the EPBD group (25.0% versus 10.1%, respectively; $P=0.0016$). Risk factors for BDS recurrence in this study were type of treatment (ES), presence of periampullary diverticula, and an in situ gallbladder with stones [6].

Several studies have reported the long-term outcomes of therapeutic ERCP for BDS removal. Risk factors for BDS included bile duct diameter [3–6,21], use of a mechanical lithotripter [22], presence of periampullary diverticula [3,6,21], brown pigment stones [4], pneumobilia [16], and treatment involving ES [6]. In particular, the status of the gallbladder was a risk factor for BDS recurrence in several studies. These studies involved ES [3,11,15,23,24] and EPBD [17], including a multicenter randomized controlled study of ES versus EPBD in Japan [6].

BDS can be divided into two groups based on stone origin: primary stones originating in the common bile duct and secondary stones originating in the gallbladder. We hypothesize that cholecystectomy reduces the incidence of pancreaticobiliary complications by preventing the occurrence of secondary stones. **Table 7** compares the recurrence rate for pancreaticobiliary complications associated with ES and EPBD. Cholecystectomy after therapeutic ERCP to treat BDS reduces the incidence of long-term complications. In particular, the recurrence rate in the EPBD group is low (4/141, 2.8%). This finding is similar to results from a prior large cohort study of EPBD [16].

The results in Group B of our study most likely reflect the occurrence of primary stones. The long-term BDS recurrence rates in patients who underwent ES or EPBD are nearly identical (ES, 21/124, 17.0%; EPBD, 4/22, 18.2%). This observation differs from those of a prior report on long-term complications in patients with a history of cholecystectomy prior to EPBD [6,25]. We hypothesize that there are a number of reasons for the difference in the recurrence rate in our study. First, the sample size in the EPBD group was relatively small; therefore, our study may be underpowered to detect differences between the two groups. Second, stone recurrences in the two groups were thought to be most likely due to primary stones. We believe that primary stones in the two groups arise from different mechanisms. In the ES group, duodenobiliary reflux and resultant bile infection play essential roles in the formation of brown pigment stones, composed mainly of calcium bilirubinate [22,26]. In the EPBD group, the primary stones may be related to incomplete clearance of residual stone fragments and unlikely spontaneous passage of minute stone fragments [16]. Loss of sphincter of Oddi function after ES and difficulties in cleaning minute stone fragments after EPBD are also thought to play a role in the generation of primary stones in each group. In our study, the procedure used to treat BDS was not found to be an independent risk factor for the recurrence of pancreaticobiliary complications. We recommend cholecystectomy for gallbladders with stones after either treatment. Pancreaticobiliary complications consist of not only BDS recurrence but also life-threatening conditions such as pancreatitis and acute cholangitis [27,28]. However, because patient age may be a relative contraindication to cholecystectomy, the proportion of patients with a gallbladder with stones who did not undergo cholecystectomy was higher in Group O (131/250, 52.4%) than in Group Y (199/960, 20.7%, $P<0.00001$). There were two main reasons why 199 patients in Group Y did not undergo cholecystectomy. First, 138 patients had one or more comorbidities (138/960, 14.4%); consequently, they were discharged from the hospital without undergoing cholecystectomy. Second, 61 patients declined cholecystectomy (61/960, 6.6%).

Since we believe that selection bias and confounding factors may influence the rate of pancreaticobiliary complication recurrence in the two groups, we selected 192 cases in each group by propensity score matching to compensate. The cumulative occurrence rate of pancreaticobiliary complications in the two propensity score-matched groups was not significantly different. It is challenging to perform cholecystectomy in patients older than age 80, especially those with comorbidities. Hazzan et al [29] reported that LC in octogenarians was safe and associated with acceptable morbidity and mortality. The mean length of hospital stay was 5.3 days and there were no mortalities. However, it is important to manage cardiovascular and pulmonary diseases. In the current study, the incidence of immediate complications such as cardiovascular or pulmonary disease was significantly higher in Group O ($P=0.0117$). However, there was no significant difference between the two groups in the incidence of acute pancreatitis, hemorrhage, acute cholangitis, acute cholecystitis, and gastrointestinal tract perforation. Therefore, we should exercise caution when selecting patients for cholecystectomy after BDS treatment, especially for those with concomitant medical diseases.

Two patients in Group Y were diagnosed with bile duct carcinoma after ES or EPBD. Long-standing loss of sphincter function might result in bacterial colonization, chronic inflammation, and the presence of cytotoxic components [30]. Multiple factors seem to be responsible for biliary carcinogenesis. It is possible that ES contributes to carcinogenesis. However, our study does not provide direct evidence for this conclusion because of the low incidence of biliary malignancies and its occurrence with both ES and EPBD.

In the current study, differences in baseline characteristics in the two groups we compared may have affected the outcomes. After multivariate analysis was performed to minimize this bias, we performed the analysis using a propensity score approach and adjusted the covariate selection in the propensity score method to produce a univariate analysis. The EPBD group also was excluded from the propensity score method. Because we performed ES in most of our octogenarian patients, we focused on patients undergoing this procedure

The current study has several limitations. The retrospective study design might have introduced an unintended bias. Because the study period spanned 1982 to 2011, some operators performed ES or EPBD using different kinds of endoscopes and accessories.

Therapeutic ERCP techniques might have improved over time. Biases from these factors remain after propensity score matching. In conclusion, a gallbladder in situ with stones was the only significant risk factor for the occurrence of pancreaticobiliary disease after treatment for BDS. However, the decision to perform cholecystectomy in octogenarians should be considered carefully. Age per se should not be the major deciding factor when selecting treatment with the goal of reducing the occurrence of pancreaticobiliary disease. Large multicenter prospective studies are needed to determine the best care after treatment for BDS in the elderly.

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