Predictive factors for outcomes of patients undergoing endoscopic therapy for bile leak after hepatobiliary surgery

Shuntaro Yabe, MD, Hironari Kato, MD*, Sho Mizukawa, MD, Yutaka Akimoto, MD, Daisuke Uchida, MD, Hiroyuki Seki, MD, Takeshi Tomoda, MD, Kazuyuki Matsumoto, MD, Naoki Yamamoto, MD, Shigeru Horiguchi, MD, Koichiro Tsutsumi, MD, Hiroyuki Okada, MD

Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan

*Corresponding author: Hironari Kato, MD

Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences

2-5-1 Shikata-cho, kita-ku, Okayama 700-8558, Japan

Tel: +81-86-235-7219 Fax: +81-86-223-5991

E-mail: katou-h@cc.okayama-u.ac.jp

Abstract

Objectives: Endoscopic procedures are used as first-line treatment for bile leak after hepatobiliary surgery. Advances have been made in endoscopic techniques and devices, but few reports have described the effectiveness of endoscopic procedures and the management principles based on the severity of bile leak. We evaluated the effectiveness of an endoscopic procedure for the treatment of bile leak after hepatobiliary surgery.

Methods: Fifty-eight patients underwent an endoscopic procedure for suspected bile leak after hepatobiliary surgery; the presence of bile leak on endoscopic retrograde cholangiopancreatography (ERCP) was evaluated retrospectively. Two groups were created based on bile leak severity at ERCP. We defined success as follows: technical, successful placement of the plastic stent at the intended bile duct; clinical, improvement in symptoms of bile leak; and eventual, disappearance of bile leak at ERCP. We evaluated several factors that influenced the success of the endoscopic procedure and the differences between bile leak severity.

Results: Success rates were as follows: technical, 90%; clinical, 79%; and eventual, 71%. The median interval between first endoscopic procedure and achievement of eventual success was 135 days (IQR, 86–257 days). Bile leak severity was the only independent factor associated with eventual success (P=0.01)

Conclusions: Endoscopic therapy is safe and effective for postoperative bile leak. Bile leak severity is the most important factor influencing successful endoscopic therapy.

Key words: bile leak, endoscopic retrograde cholangiopancreatography, hepatobiliary surgery, living donor liver transplantation, liver resection

Introduction

Bile leak is one of the most serious adverse events after hepatobiliary surgery. Despite improvements in surgical techniques, adverse events rates have not changed[1] and bile leak occurs in 3% to 18% of patients after hepatobiliary surgery.[2-8]

Bile in the dead space after hepatobiliary surgery predisposes patients to sepsis development by providing a favorable environment for the invasion and growth of bacteria, which is a well-known cause of liver failure and death.[9-11] Several surgical, percutaneous, and endoscopic treatments have been proposed for these cases. Surgical reinterventions in these cases are invasive and have mortality rates as high as 38%.[11] Percutaneous transhepatic biliary drainage (PTBD) can lead to resolution of bile leak in 44% to 70% patients.[12,13] However, a PTBD catheter has to be kept in the body for several months, which is invasive and negatively influences quality of life.

With advances in endoscopic techniques and devices, endoscopic procedures associated with endoscopic retrograde cholangiopancreatography (ERCP) can identify the bile leak site in 84% to 98% of patients[7,8,14,15] and have become alternative therapeutic options for bile leak management. Few reports have described the effectiveness of endoscopic therapy and factors influencing endoscopic therapy outcomes. Bile leak location is an important factor influencing the success of endoscopic therapy.[16] However, no reports have described the management principles based on bile leak severity or long-term outcomes after successful endoscopic therapy. This study evaluated the effectiveness

of endoscopic therapy in the treatment of bile leak after hepatobiliary surgery, evaluated the long-term outcomes after successful endoscopic therapy, and identified factors (such as severity of bile leak) influencing the outcome of endoscopic procedures.

Patients and Methods

Patients

Sixty-seven consecutive patients underwent endoscopic procedures for suspicion of bile leak after hepatobiliary surgery between July 2004 and June 2014 at Okayama University Hospital. Patients with fever, abdominal pain, inflammatory response, increasing white blood cell count or C-reactive protein (CRP) level, and/or abnormal biochemical test results for hepatobiliary enzymes after hepatobiliary surgery underwent radiological studies such as abdominal ultrasound, computed tomography, and/or magnetic resonance cholangiopancreatography. Patients with possible bile leak as determined by these radiological studies and/or with increasing bilious output from a transabdominal drain placed during surgery were referred for ERCP. Bile leak was determined during ERCP in 58 of these 67 patients. These 58 were included in this retrospective study, which was approved by the Okayama University School of Medicine Clinical Ethics Committee on Human Experiments in accordance with the Helsinki Declaration.

Endoscopic procedure and bile leak severity

All endoscopic procedures were performed by experienced endoscopists using a JF260V or TJF260V duodenoscope (Olympus Optical Co, Ltd, Tokyo Japan) with a working channel diameter of more than 3.7 mm, through which most devices could pass.

All patients were consciously sedated by intravenous drug administration. After selective biliary cannulation, a cholangiogram was performed. Bile leak was defined as the leakage of contrast material from somewhere such as biliary anastomosis, stump of the bile duct or cystic duct, or stump of the liver resection as determined by fluoroscopy. The extravasation site was identified and endoscopic intervention was performed.

We classified patients undergoing ERCP into two groups according to bile leak severity. Dechene et al[17] reported a two-category grading system proposed for bile leak severity; the categories were small leak and large leak. Bile leak was classified as small if the leak from the biliary tract was observed only after complete filling of the intrahepatic bile duct with contrast agent (Fig. 1); it was classified as large if the leak from the biliary tract was observed as substantial extravasation before complete filling of the intrahepatic bile duct with contrast agent (Fig. 2).

We attempted to cover the segment of bile duct from where the leak originated with a plastic stent (Fig. 3A, B). The length and type of stent were determined according to the bile leak location. A conventional 7-Fr plastic stent was placed across the sphincter of Oddi in normal cases; a 5-Fr stent or 6-Fr stent was placed when the bile duct at the proximal side of the location of the bile leak was thin. Endoscopic sphincterotomy could reduce the transpapillary biliary pressure gradient, which was helpful for closure of the fistula because of due to the decrease in bile leak. However, it would cause reflux of duodenal fluid containing bacteria and increase the risk of reflux cholangitis and biliary

stones in the long term. Therefore, we only performed endoscopic sphincterotomy in cases of multiple stent placements. When the intrahepatic duct proximal to the bile leak location was too thin to place small-bore plastic stents in the case of bile leak from the peripheral duct or cut stump of the liver, the plastic stent was placed at the bile duct on the distal side of the bile leak (Fig. 3C). When the bile leak location was on the proximal side of the biliary stricture, we placed a plastic stent over the site of the biliary stricture. We used an inside stent for cases of bile leak complicated by severe biliary stricture after LDLT to prevent reflux cholangitis[18,19]. We could not use self-expandable metallic stents (SEMS) in any cases because of the health insurance in Japan.

Outcome assessment

Technical success was identification of the bile leak site and successful placement of the plastic stent at the intended bile duct. Clinical success was improvement of the clinical symptoms of bile leak (fever, abdominal pain, etc.). If clinical success could not be achieved within a few days after plastic stent placement, then we retried ERCP for re-evaluation and stent replacement. If it could not be achieved despite stent replacement, then we performed endoscopic nasobiliary drainage (ENBD). A few weeks after achieving clinical success with ENBD, we exchanged the ENBD tube for a conventional plastic stent. If we were able to achieve clinical success, then we scheduled follow-up ERCP after 2 to 3 months. Endoscopic therapy was considered successful when the leak

could not be identified after complete filling of the intrahepatic bile duct with contrast agent, which we defined as eventual success.

After eventual success, we frequently replaced the plastic stent for the biliary stricture associated with bile leak. We scheduled follow-up ERCP and replacement of the plastic stent until resolution of the biliary stricture.

If technical success, clinical success, or eventual success achievement by only using endoscopic therapy was difficult, then percutaneous transhepatic biliary drainage (PTBD) or reoperation was performed. We retrospectively evaluated patient characteristics, endoscopic procedure details, and differences between the small and large leak groups with eventual success.

Statistical analysis

Continuous variables are presented as median and range or interquartile range (IQR). Comparison of continuous variables was performed using the Wilcoxon signed-rank test; comparison of dichotomous variables was performed using the Fisher exact test. Logistic regression analysis was performed to identify any significant factor influencing endoscopic procedure outcomes for postoperative bile leak. $P<0.05$ was statistically significant. JMP 10.0.0 statistical software (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

Results

Patient characteristics and endoscopic procedure details

Patient characteristics and endoscopic procedures details are shown in Table 1. The median follow-up period was 910 days (range, 19–3775 days).

The underlying diagnoses for living donor liver transplantation (LDLT) were liver cirrhosis (n=21), hepatocellular carcinoma (n=7), and acute hepatitis (n=1); those for liver resection were hepatocellular carcinoma (n=22), cholangiocellular carcinoma (n=2), liver metastasis (n=2), LDLT donor (n=1), liver cyst (n=1), and other disease (n=1). The most frequent location of extravasation of contrast material during procedures for patients after LDLT was the anastomosis, and that after liver resection was the hilar duct. Biliary stricture was diagnosed in 36 patients (62%). All these strictures were caused by damage influenced by surgery and scarring during the healing process after bile leak. Locations of biliary stricture were the anastomosis for biliary reconstruction after LDLT (n=21), hilar duct (n=11), and peripheral duct (n=4). During the first endoscopic procedure, 43 patients (including eight patients subjected to an inside stent) had one plastic stent placed and nine patients (including one patient subjected to inside stents) had two plastic stents placed. Adverse events after endoscopic therapy developed in six patients. Four patients had pancreatitis as early adverse events but improved with conservative treatment. The other two patients had intrahepatic stones, which were considered late adverse events and were removed endoscopically.

Success rates and long-term outcomes

Figure 4 shows the detailed flow diagram of endoscopic therapy. Of 58 patients with bile leak detected by ERCP, 52 (90%) achieved technical success. In the remaining six patients with technical failure, a guidewire could not be inserted into the proximal bile duct across the location of the bile leak. These six patients underwent PTBD (n=3) or reoperation (n=3). In the group with technical success, 46 (79%) patients achieved clinical success; however, six patients (including one patient who was finally subjected to ENBD) needed PTBD (n=4) or reoperation (n=2). The median interval between the first endoscopic procedure and achievement of clinical success was 2.5 days (IQR, 1–8.8).

Thirty-eight out of 46 (83%) patients had clinical success after the first endoscopic procedure. The other eight patients underwent additional endoscopic procedures with changes in the size, length, number, and/or site of the stent; seven of these patients required two sessions and the other required four sessions to achieve clinical success, including two patients subjected to ENBD.

Of the 46 patients with clinical success, 41 (71%) achieved eventual success at a median of 135 days (IQR, 86–257 days) and five died of other postoperative adverse events or deterioration with underlying disease. The median number of sessions required for eventual success was two (IQR, 2–3). Thirty-five of 41 patients with eventual success had intra-abdominal drainage during the first procedure; all 35 were relieved of the intra-

abdominal drainage during stent placement or immediately after stent removal because of achieving eventual success.

Figure 5 shows long-term outcomes. We replaced plastic stents because of biliary stricture in 20 of 41 patients after achieving eventual success. The remaining 21 patients were stent-free immediately after achieving eventual success and withdrawal of intra-abdominal drainage. Sixteen of 20 patients with replacement of plastic stents were stent-free at a median of 312 days (IQR, 124–553 days). After achieving stent-free status, no patients had bile leak recurrence. However, one patient had biliary stricture recurrence, so we placed a plastic stent over this site. The other four patients underwent stent placement because of severe stricture at a median of 641 days (IQR, 434–748 days). The biliary stricture location in these three patients was the anastomosis; it was the hilar duct in the other patient. Finally, 36 of 58 (62%) patients completed endoscopic therapy at a median of 323 days (IQR, 110–537 days).

Factors influencing outcome

To identify factors influencing eventual success, we analyzed several factors between patients with eventual success (group A) and patients without eventual success (group B) (Table 2).

Univariate analysis revealed CRP (P=0.04) and bile leak severity (P=0.02) as variables. Multivariate analysis revealed bile leak severity as an independent factor

associated with eventual success (OR, 7.0; 95% CI, 1.66–48.51; *P*=0.01)

Comparison between the small leak and large leak groups

In the group achieving eventual success, we compared the interval and the number of sessions required to achieve each success for the small leak and large leak groups (Table 3).

Median intervals between achieving clinical success and eventual success for the small leak group were significantly shorter than those for the large leak group. In addition, the median numbers of sessions to achieve clinical success and eventual success in the small leak group were also significantly smaller than those in the large leak group.

Table 4 shows the success rate for improvements in the small leak and large leak groups. The technical success rate in the small leak group (24/24, 100%) was significantly higher than that in the large leak group (28/34, 82.3%) (*P*=0.04). We hypothesize that it was difficult to find the bile duct and then insert the guidewire into the bile duct proximal to the location of the bile leak because the fistula was larger and successful enhancement of the proximal bile duct using contrast material can be achieved less frequently in a large leak group than in a small leak group. There was no significant difference in clinical and eventual success between the small leak and large leak groups once technical success was achieved.

Discussion

Endoscopic procedures associated with ERCP are the initial treatment for bile leak after hepatobiliary surgery but little has been reported regarding its effectiveness. For postoperative bile leak treatment, endoscopic procedures are less invasive than PTBD. Efficacy of PTBD for bile leak after LDLT was evaluated,[12] resulting in technical and clinical success rates of 91% and 70%, respectively. However, 6 of 14 patients (43%) who underwent PTBD catheter removal experienced jaundice or cholangitis due to biliary stricture. In this study, 1 out of 37 patients (3%) experienced biliary stricture after stent removal. In addition, the median duration of PTBD catheter use was 8 months (range, 5–20 months), which was longer than the duration of intra-abdominal drainage in our study (median, 45 days; IQR, 20–93 days). Long-term placement of percutaneous drainage tubes can result in serious patient discomfort or infection. Therefore, endoscopic procedures can decrease the morbidity of biliary stricture and shorten the percutaneous drainage period.

The endpoint in most reports regarding endoscopic therapy for postsurgical bile leak was resolution of clinical symptoms associated with bile leak. We achieved clinical success in 46 of 58 patients (79%), similar to previous reports.[5-8,14-17,20] In addition, we analyzed long-term outcomes after clinical success. Biliary stricture frequently occurred with bile leak and required long-term stent placement, depending on the stricture severity.

Several reports have described factors influencing endoscopic therapy outcomes

for postoperative bile leak. Patients in the large leak group were less likely to achieve success with endoscopic procedures, although this was not statistically different.[17] They proposed that patients with leakage from the common hepatic duct were less likely to achieve success with endoscopic procedures. Bile leak location was the most important factor influencing endoscopic procedure success.[16] Successful treatment of T-tube tract bile leak after liver transplantation was reported for 20 out of 21 patients (95%); bile leak from the anastomosis was successfully treated in three out of seven patients (43%) (P=0.01).[7] This study showed no significant difference in the rate of successful endoscopic therapy, depending on the location of bile leak, possibly because of the smaller number of patients with bile leak from the cystic duct or common hepatic duct.

Bile leak severity was an independent factor associated with successful endoscopic therapy during multivariate analysis. In addition, there were significant differences in the stent placement interval and the number of procedures required to achieve clinical and eventual success between the large leak and small leak groups. Although a large leak was less likely to be resolved than a small leak, considering these data, comparisons between the large leak and small leak groups indicated that once technical success had been achieved, we could expect bile leak improvement at approximately the same rate regardless of severity.

This study had limitations. It was a retrospective, single-center analysis with a relatively small number of patients included. Therefore, the number of patients with bile

leak from each location was not enough to evaluate statistically. The numbers of patients with bile leak from the common hepatic duct, which influenced the outcome of endoscopic therapy in other reports, and from the cystic duct were too small to evaluate statistically. Finally, we could not evaluate the effectiveness of SEMS because Japanese health insurance does not allow these for bile leak after hepatobiliary surgery. Several reports described the effectiveness of SEMS in patients with bile leak from the common bile duct.[21-24] If we could use SEMS for patients with bile leak from the cystic duct remnant after LDLT and from the common hepatic duct after liver resection, then the success rate of endoscopic therapy might become higher and the duration of stent deployment might become shorter. However, it is controversial to place SEMS into the narrow peripheral bile duct because of obstruction of the bile duct branch and over-dilation.

Our study shows that endoscopic therapy with plastic stent placement with or without endoscopic sphincterotomy is safe and effective for postoperative bile leak, and that bile leak severity is the most important factor influencing its eventual success. Technical success is significantly more difficult in patients with a large bile leak. Long-term outcomes are favorable but stents cannot be removed for a long time if patients have biliary stricture after resolution of bile leak.

Conflict of interests

The authors declare no conflict of interests for this article.

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Figure Legends

Figure 1. Small leak.

A: Retrograde cholangiogram shows only complete filling of the intrahepatic bile ducts before bile leak was detected.

B: Bile leak of contrast agent is shown on retrograde cholangiogram only after complete filling of the intrahepatic bile ducts.

Figure 2. Large leak.

Substantial extravasation of the contrast agent is shown by retrograde cholangiogram before complete filling of the intrahepatic bile duct.

Figure 3. Location of the bile leak and site of the plastic stent.

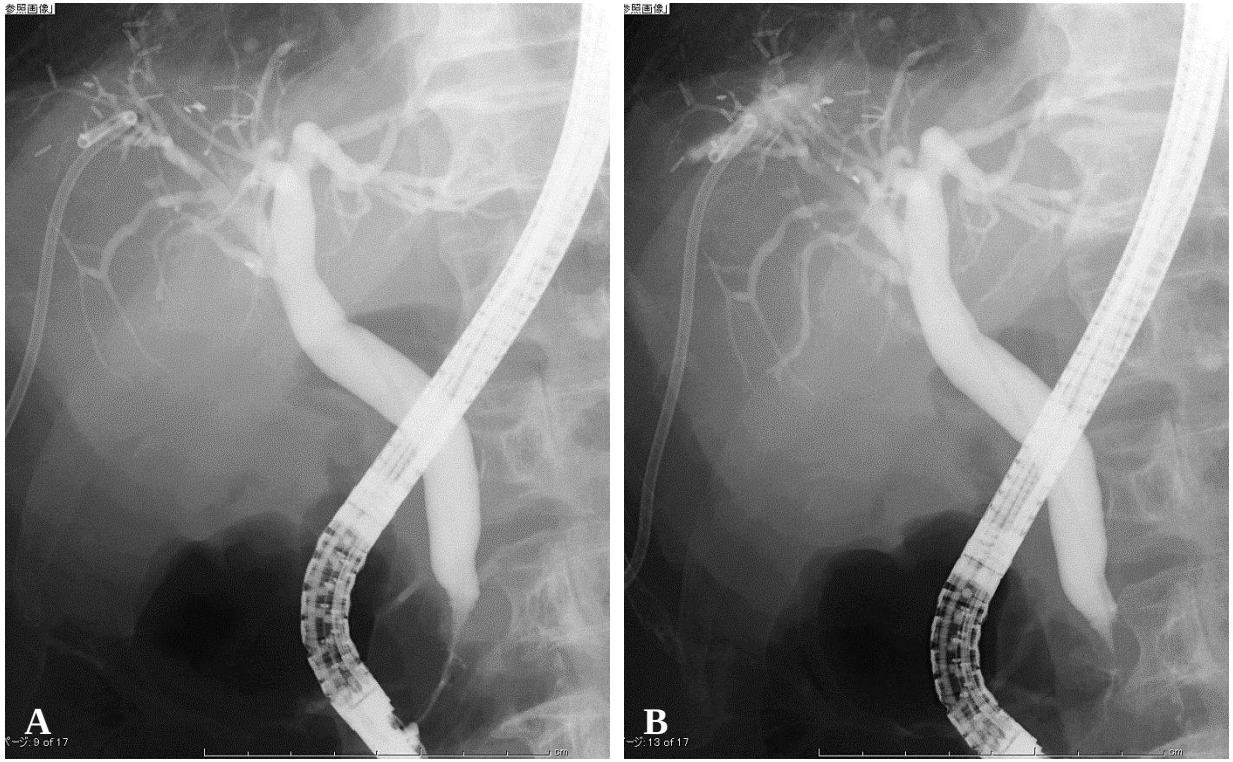
A: Leak from the hilar duct and plastic stent placed to cover the segment of the bile duct where the leak originated.

B: Leak from the anastomosis and plastic stent placed to cover the segment of bile duct where the leak originated.

C: Leak from the peripheral duct and plastic stent placed at the bile duct distal to where the leak originated.

Figure 4. Flow diagrams and results of the management of bile leaks.

Figure 5. Long-term outcome after achieving eventual success.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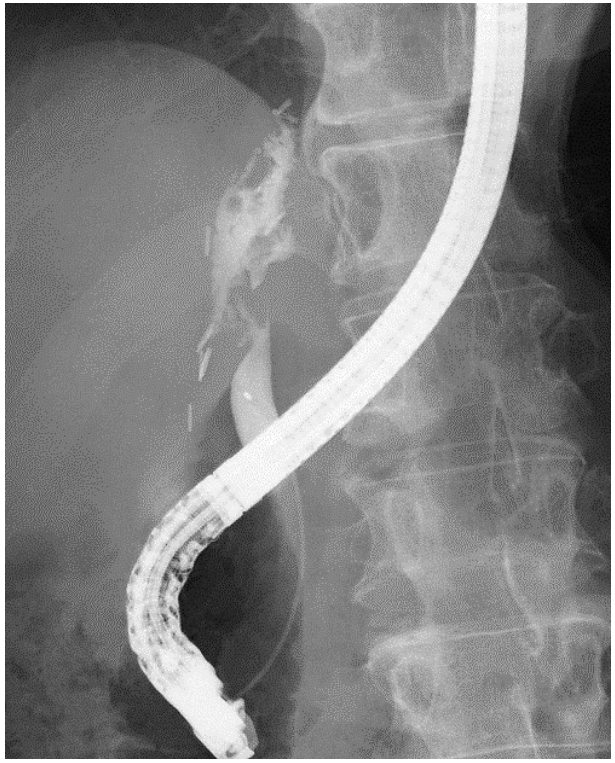

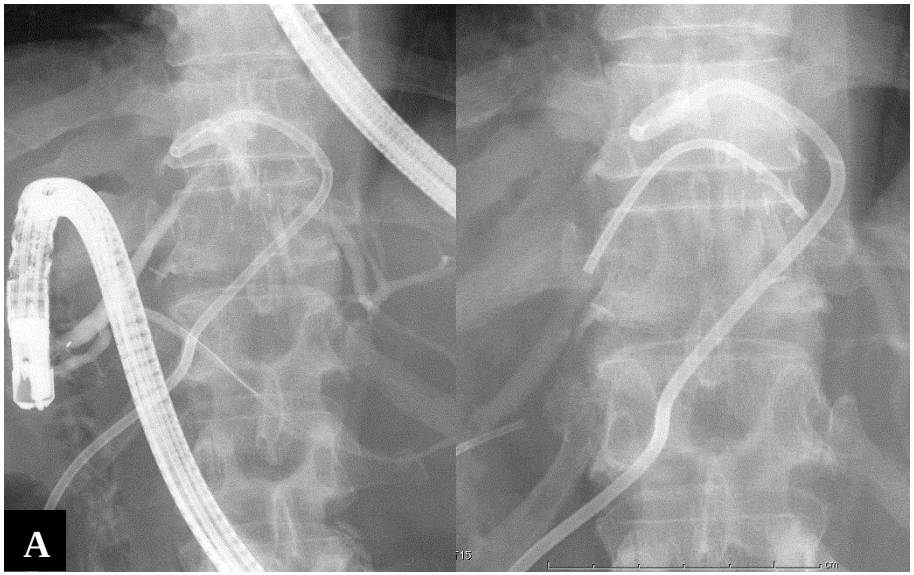
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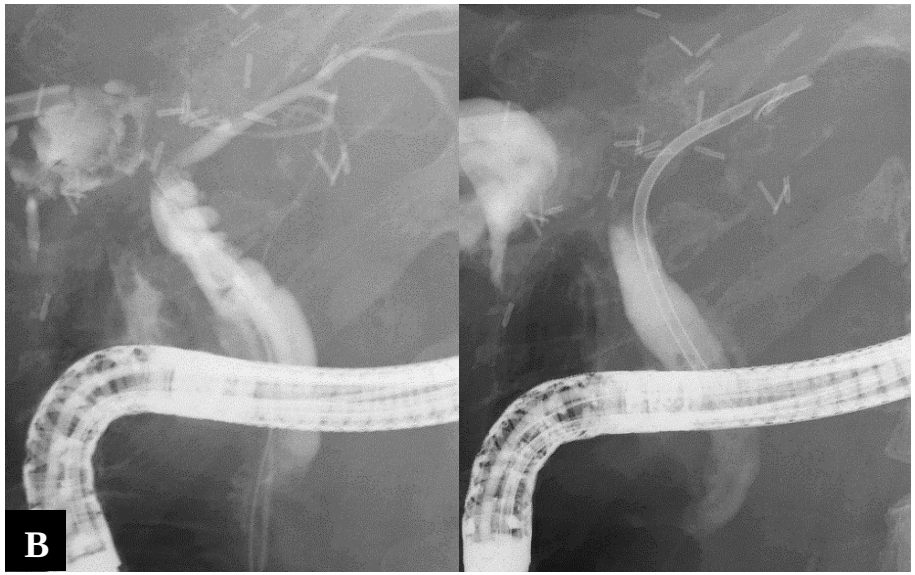
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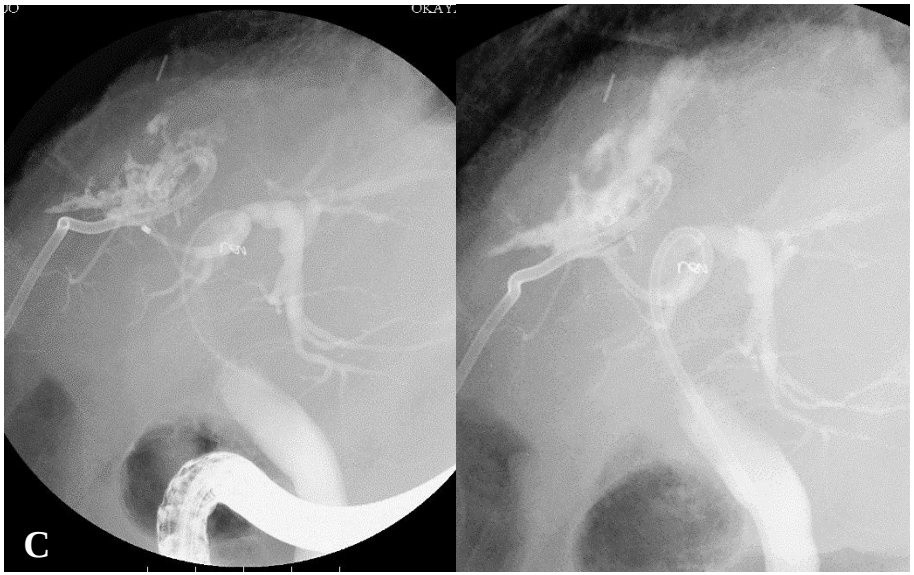
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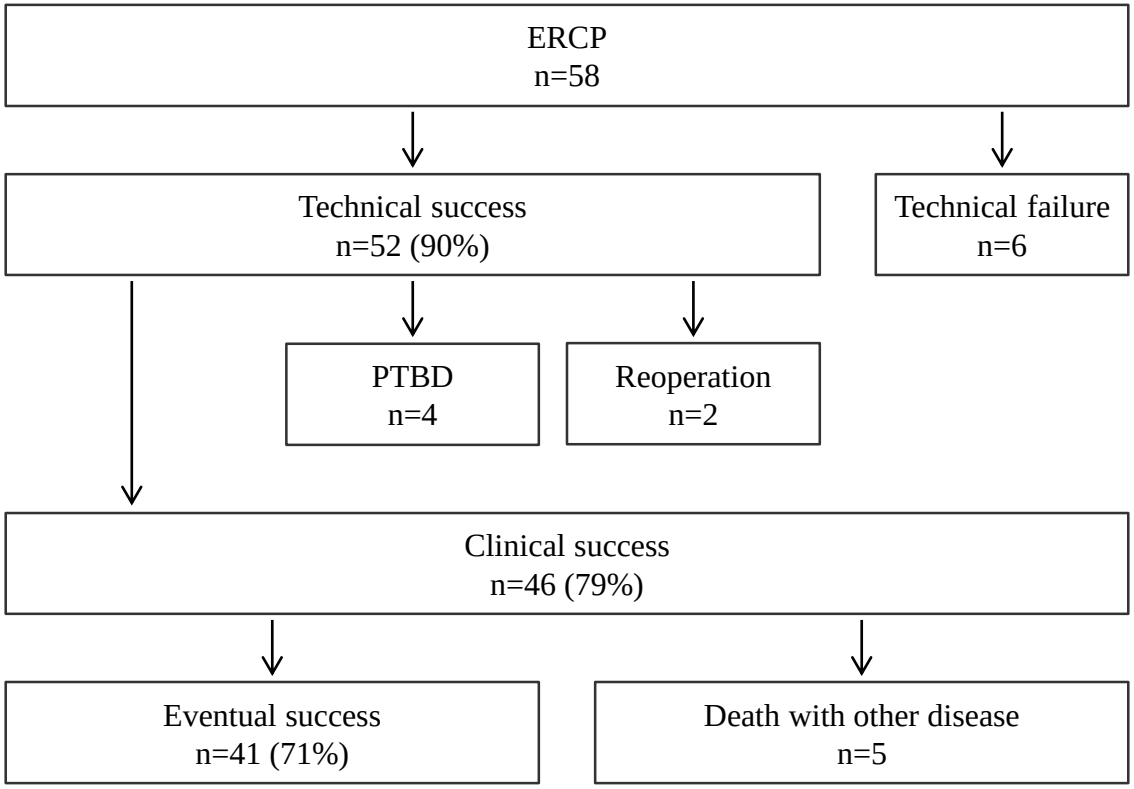
ERCP
n=58
Technical success
n=52 (90%)
Technical failure
n=6
PTBD
n=4
Reoperation
n=2
Clinical success
n=46 (79%)
Eventual success
n=41 (71%)
Death with other disease
n=5

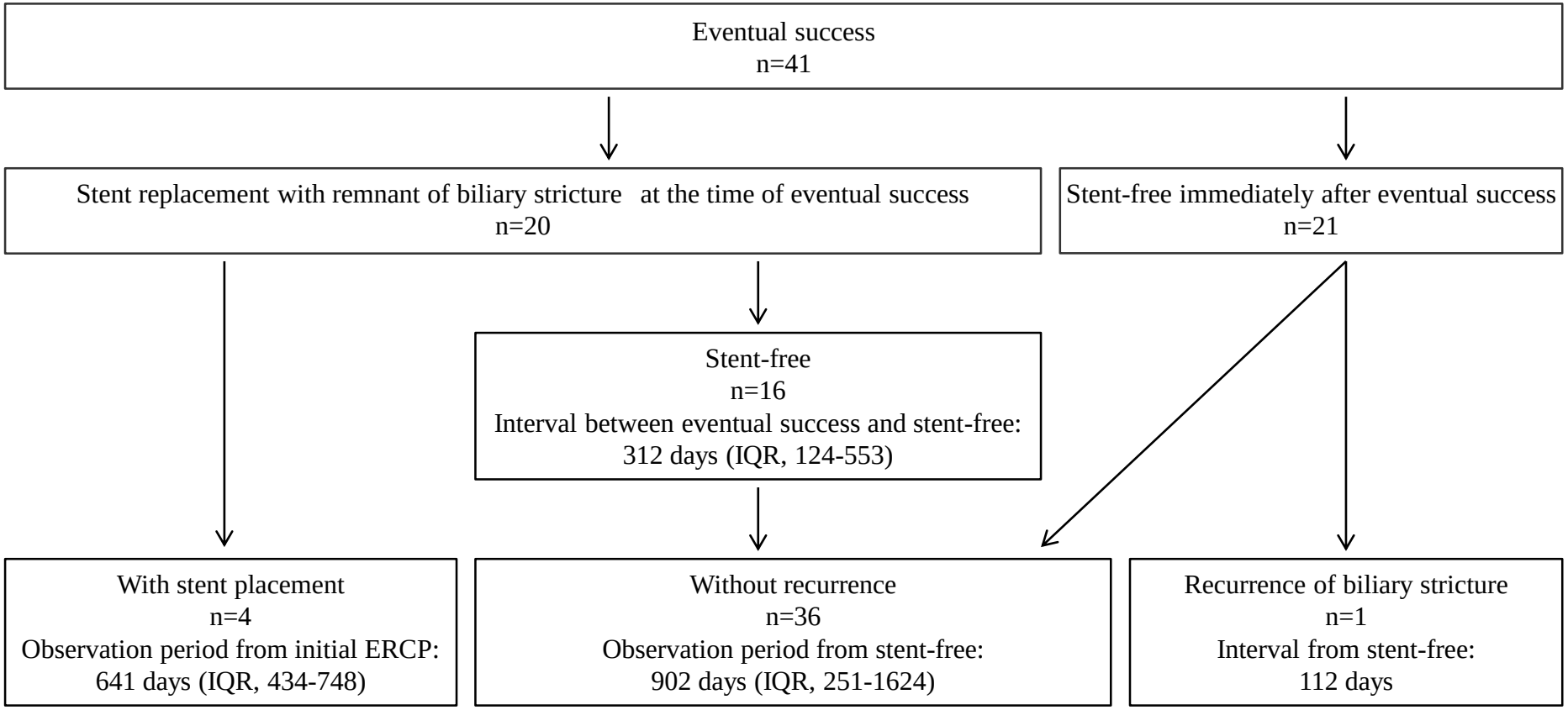
Eventual success
n=41
Stent replacement with remnant of biliary stricture at the time of eventual success
n=20
Stent-free immediately after eventual success
n=21
Stent-free
n=16
Interval between eventual success and stent-free:
312 days (IQR, 124-553)
With stent placement
n=4
Observation period from initial ERCP:
641 days (IQR, 434-748)
Without recurrence
n=36
Observation period from stent-free:
902 days (IQR, 251-1624)
Recurrence of biliary stricture
n=1
Interval from stent-free:
112 days

Table 1. Patient characteristics and details of endoscopic procedures

N		58
Sex, male		43 (74%)
Age, y (range)		60 (21–78)
Surgery type	LDLT	29
	Right lobe graft	18
	Left lobe graft	8
	Posterior segment graft	3
	Liver resection	29
	Right lobe resection	15
	Left lobe resection	11
	Other	3
Interval between surgery and the first procedure, d (range)		47 (5–234)
Bile leak locations		
LDLT	Anastomosis	25
	Cystic duct remnant	4
	CHD	1
LR	Hilar duct	17
	Peripheral duct	11
Biliary stricture		36 (62%)
Bile leak severity		

Small leak	24 (41%)
Large leak	34 (59%)
Endoscopic sphincterotomy	17 (29%)

LDLT, living donor liver transplantation; CHD, common hepatic duct.

Table 2. Analysis of factors influencing achievement of eventual success

	Univariable analysis			Multivariate analysis		
	Group A	Group B	*P*	OR	95% CI	*P*
N	41 (71%)	17 (29%)				
Sex, male	30 (73%)	13 (76%)	0.79			
Age, y (range)	59 (21–78)	63 (33–77)	0.08			
Laboratory test results before ERCP, median (range)						
WBC, $\times 10^3/\mu L$ (IQR)	4.4 (3.3–6.2)	6.0 (4.2–7.6)	0.18			
AST, U/L (IQR)	30 (24–64)	45 (25–80)	0.41			
ALT, U/L (IQR)	35 (21–71)	39 (18–76)	0.84			

γ-GTP, IU/L (IQR)	96 (55–210)	102 (55–540)	0.37			
T-Bil, mg/dL (IQR)	0.9 (0.6–1.7)	1.2 (0.7–6.3)	0.09			
CRP, mg/dL (IQR)	1.6 (0.6–3.0)	2.9 (1.5–5.4)	0.04	1.1	0.91–1.31	0.35
Surgery type			0.77			
LDLT	21	8				
Liver resection	20	9				
Interval between surgery and first procedure, d (range)	48 (5–234)	45 (20–127)	0.5			
Location of bile leak			0.64			
LDLT Anastomosis	18	7				
LDLT Cystic duct remnant	3	1				

	CHD	0	1				
LR	Hilar duct	12	5				
	Peripheral duct	8	3				
Biliary stricture		28	8	0.45			
Severity of bile leak				0.02	7	1.66–48.51	0.01
	Small leak	21	3				
	Large leak	20	14				
Endoscopic sphincterotomy		10	7	0.21			

Group A, patients with eventual success; Group B, patients without eventual success; OR, odds ratio; CI, confidence interval; IQR, interquartile range; AST, aspartate amino transferase; ALT, alanine amino

transferase; GTP, guanosine triphosphate; CRP, C-reactive protein; LDLT, living donor liver transplantation; LR, liver resection; CHD, common hepatic duct.

Table 3. Comparison between the small leak group and large leak group in the eventual success group

	Small leak group	Large leak group	*P*
N	21	20	
Interval between first procedure and clinical success, d (IQR)	2 (1–4.75)	4.5 (2–12.5)	0.04
Sessions from the first procedure to clinical success, n (IQR)	1 (1–1)	1 (1–2)	0.02
Interval between the first procedure and eventual success, d (IQR)	124 (81–164)	198 (90–381)	0.04
Sessions from the first procedure to eventual success, n (IQR)	2 (2–2)	3 (2–5)	<0.01

IQR, interquartile range.

Table 4. Success rate of each improvement for the small leak group and large leak group

	Small leak group	Large leak group	*P*
N	24	20	
Technical success, % (n/N)	100 (24/24)	82.3 (28/34)	0.04
Clinical success rate for the group who achieved technical success, % (clinical success, n/technical success, n)	95.8 (23/24)	82.1 (23/28)	0.12
Eventual success rate for the group who achieved clinical success, % (eventual success, n/clinical success, n)	91.3 (21/23)	87.0 (20/23)	0.64